10523015.trn

AUTHOR(S): Kim, Hui Hyun; Ji, Hye Young; Lee, Hye Won; Kim, Soon Ai; Lee, Seonkyoung; Yi, Kyu Yang; Lee, Hye Suk
CORPORATE SOURCE: Drug Metabolism and Bioanalysis Laboratory, College of Pharmacy and Medicinal Resources Research Institute, Wonkwang University, Iksan, S. Korea
SOURCE: Drug Development Research (2006), Volume Date 2005, 66(1), 40-49
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The in vitro metabolism and the transport of a novel anti-angiogenic agent KR-31831, (2R,3R,4S)-6-amino-4-[N-(4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)amino]-3-hydroxy-2-dimethyoxymethyl-3,4-dihydro-2-methyl-2H-1-benzopyran were investigated. Liquid chromatog.-mass spectrometry and tandem mass spectrometry were used for qual. and quant. anal. The bidirectional transport studies of KR-31831 using Caco-2 cell monolayers showed the efflux to be significantly higher than influx (29.1+10-6 compared to 11.5+10-6 cm/s). P-glycoprotein inhibitors significantly increased the influx of KR-31831 and decreased the efflux of KR-31831. These data indicate that KR-313831 is a substrate for an efflux pump, P-glycoprotein. The incubations of KR-31831 with human liver microsomes produced three metabolites, M1, M2, and M3. M1 and M2 were identified as N-(4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)amine and (2R,3R,4S)-6-amino-4-N-(4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)aminol-3-hydroxy-2-hydroxymethyl-3,4-dihydro-2-methyl-2H-1-benzopyran by comparison with the authentic stds. M3 was tentatively characterized as hydroxy-KR-31831. CYP3A4 was identified as the major enzyme responsible for KR-31831 metabolism to a major metabolite M1 using the combination of correlation anal., immuno-inhibition, chemical inhibition in human liver microsomes, and metabolism by cDNA expressed CYP enzymes. There is the possibility of drug-drug interactions when prescribing KR-31831 concomitantly with known inhibitors or inducers of CYP3A4 and P-glycoprotein. KR-31831 was found to inhibit potently the metabolism of CYP2D6 substrate, suggesting that coadministration of KR-31831 with CYP2D6 substrates may have significant effects on the pharmacokinetics of CYP2D6 substrates.
IT 571141-49-6, KR-31831
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(characterization of cytochrome P 450 enzymes and P-glycoprotein involved in metabolism and transport of a new anti-angiogenic agent KR-31831)
RN 571141-49-6 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-(CA INDEX NAME)

Absolute stereochemistry.

10523015.trn

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LOGINID:SSSPTA1626GMS

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	JAN 08	CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS 3	JAN 16	CA/CAplus Company Name Thesaurus enhanced and reloaded
NEWS 4	JAN 16	IPC version 2007.01 thesaurus available on STN
NEWS 5	JAN 16	WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS 6	JAN 22	CA/CAplus updated with revised CAS roles
NEWS 7	JAN 22	CA/CAplus enhanced with patent applications from India
NEWS 8	JAN 29	PHAR reloaded with new search and display fields
NEWS 9	JAN 29	CAS Registry Number crossover limit increased to 300,000 in multiple databases
NEWS 10	FEB 15	PATDPASPC enhanced with Drug Approval numbers
NEWS 11	FEB 15	RUSSIAPAT enhanced with pre-1994 records
NEWS 12	FEB 23	KOREAPAT enhanced with IPC 8 features and functionality
NEWS 13	FEB 26	MEDLINE reloaded with enhancements
NEWS 14	FEB 26	EMBASE enhanced with Clinical Trial Number field
NEWS 15	FEB 26	TOXCENTER enhanced with reloaded MEDLINE
NEWS 16	FEB 26	IFICDB/IFIPAT/IFIUDB reloaded with enhancements
NEWS 17	FEB 26	CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases
NEWS 18	MAR 15	WPIDS/WPIX enhanced with new FRAGHITSTR display format
NEWS 19	MAR 16	CASREACT coverage extended
NEWS 20	MAR 20	MARPAT now updated daily
NEWS 21	MAR 22	LWPI reloaded
NEWS 22	MAR 30	RDISCLOSURE reloaded with enhancements
NEWS 23	MAR 30	INPADOCDB will replace INPADOC on STN
NEWS 24	APR 02	JICST-EPLUS removed from database clusters and STN

NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN  Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:33:24 ON 20 APR 2007

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files.  For example, the EXPAND
command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'REGISTRY' ENTERED AT 14:33:37 ON 20 APR 2007
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STRUCTURE FILE UPDATES:   19 APR 2007  HIGHEST RN 931104-30-2
DICTIONARY FILE UPDATES:  19 APR 2007  HIGHEST RN 931104-30-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10523015.str
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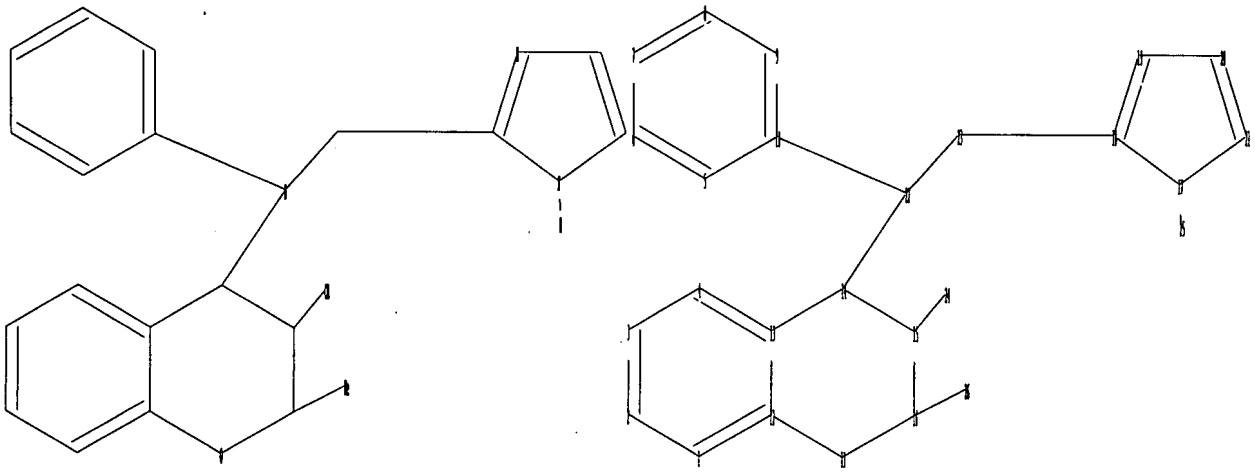
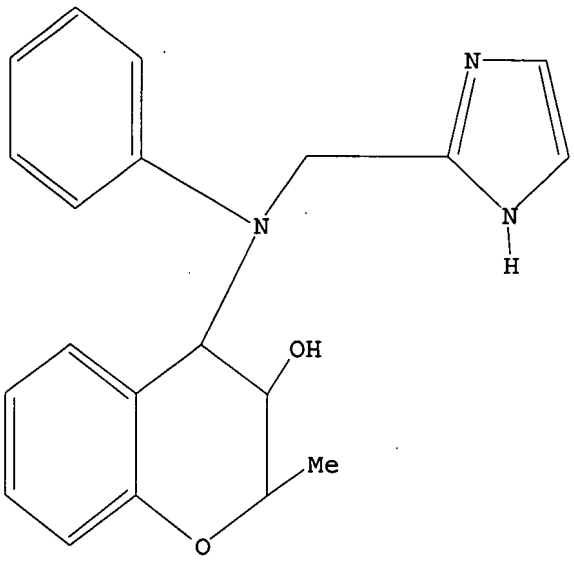


chain nodes :
22 23 24 25 26
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
chain bonds :
10-22 14-22 15-24 16-26 17-25 18-23 22-23
ring bonds :
1-2 1-12 2-3 3-4 4-13 5-6 5-10 6-7 7-8 8-9 9-10 11-12 11-16 12-13
13-14 14-15 15-16 17-18 17-21 18-19 19-20 20-21
exact/norm bonds :
10-22 14-22 15-24 17-18 17-21 18-19 19-20 22-23
exact bonds :
11-12 11-16 13-14 14-15 15-16 16-26 17-25 18-23 20-21
normalized bonds :
1-2 1-12 2-3 3-4 4-13 5-6 5-10 6-7 7-8 8-9 9-10 12-13
isolated ring systems :
containing 1 : 5 : 17 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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=> s l1
SAMPLE SEARCH INITIATED 14:33:53 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -       11 TO ITERATE

100.0% PROCESSED       11 ITERATIONS                              4 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:           22 TO      418
PROJECTED ANSWERS:               4 TO      200

L2             4 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 14:33:59 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      259 TO ITERATE

100.0% PROCESSED      259 ITERATIONS                             71 ANSWERS
SEARCH TIME: 00.00.01

L3            71 SEA SSS FUL L1

=>
Uploading C:\Program Files\Stnexp\Queries\10523015a.str
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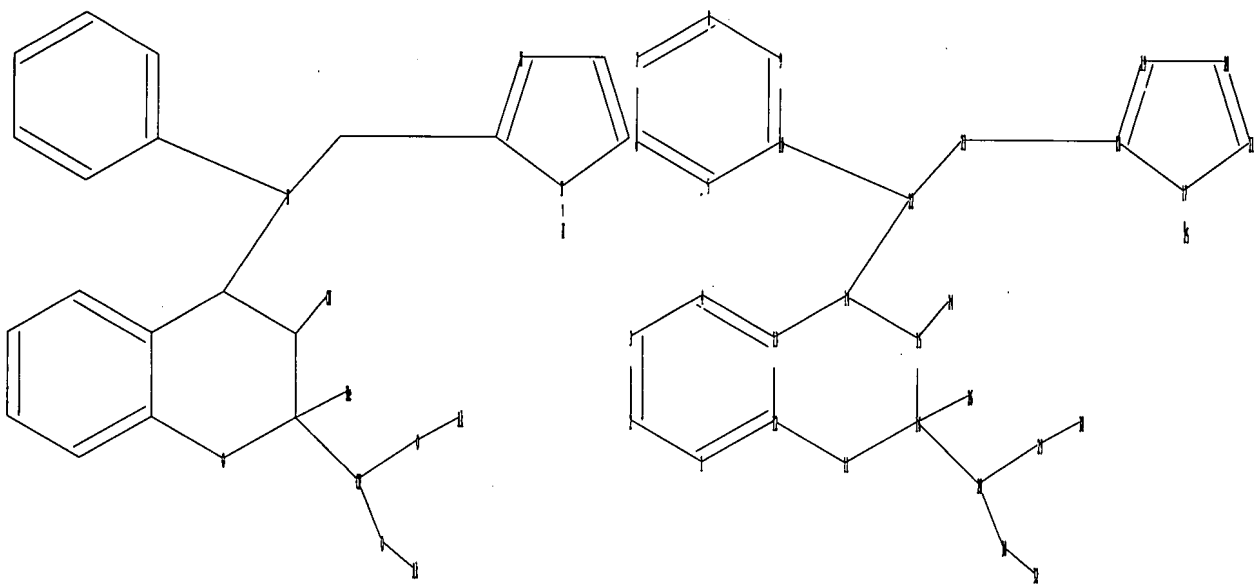
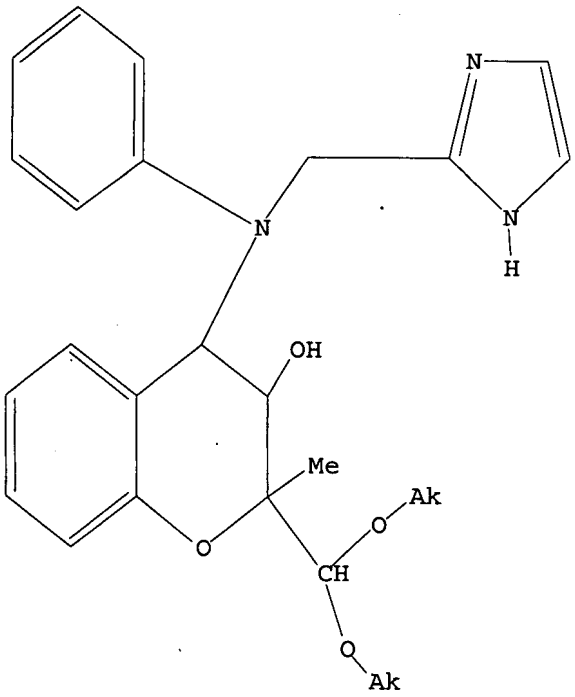


chain nodes :
22 23 24 25 26 28 29 30 31 32
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
chain bonds :
10-22 14-22 15-24 16-26 16-28 17-25 18-23 22-23 28-29 28-30 29-31 30-32
ring bonds :
1-2 1-12 2-3 3-4 4-13 5-6 5-10 6-7 7-8 8-9 9-10 11-12 11-16 12-13
13-14 14-15 15-16 17-18 17-21 18-19 19-20 20-21
exact/norm bonds :
10-22 14-22 15-24 17-18 17-21 18-19 19-20 22-23 28-29 28-30 29-31 30-32
exact bonds :
11-12 11-16 13-14 14-15 15-16 16-26 16-28 17-25 18-23 20-21
normalized bonds :
1-2 1-12 2-3 3-4 4-13 5-6 5-10 6-7 7-8 8-9 9-10 12-13
isolated ring systems :
containing 1 : 5 : 17 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 28:CLASS
29:CLASS 30:CLASS 31:CLASS 32:CLASS

L4 STRUCTURE UPLOADED

=> d l4
L4 HAS NO ANSWERS
L4 STR



Structure attributes must be viewed using STN Express query preparation.

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=> s l4
SAMPLE SEARCH INITIATED 14:36:51 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        7 TO ITERATE

100.0% PROCESSED         7 ITERATIONS                                 4 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            7 TO      298
PROJECTED ANSWERS:               4 TO      200

L5             4 SEA SSS SAM L4

=> s l4 sss full
FULL SEARCH INITIATED 14:36:58 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      166 TO ITERATE

100.0% PROCESSED      166 ITERATIONS                                52 ANSWERS
SEARCH TIME: 00.00.01

L6            52 SEA SSS FUL L4

=> FIL HCAPLUS
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     346.00     346.21

FILE 'HCAPLUS' ENTERED AT 14:37:03 ON 20 APR 2007
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FILE COVERS 1907 - 20 Apr 2007 VOL 146 ISS 18
FILE LAST UPDATED: 19 Apr 2007 (20070419/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d his

     (FILE 'HOME' ENTERED AT 14:33:24 ON 20 APR 2007)

     FILE 'REGISTRY' ENTERED AT 14:33:37 ON 20 APR 2007
L1             STRUCTURE UPLOADED
L2           4 S L1
L3          71 S L1 SSS FULL
L4             STRUCTURE UPLOADED
L5           4 S L4
L6          52 S L4 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 14:37:03 ON 20 APR 2007

=> s l3
L7          32 L3

=> s l6
L8           8 L6

=> s l7 and py<=2002
      22870547 PY<=2002
L9          12 L7 AND PY<=2002

=> s l8 and py<=2002
      22870547 PY<=2002
L10          0 L8 AND PY<=2002

=> d l8 ibib abs hitstr tot

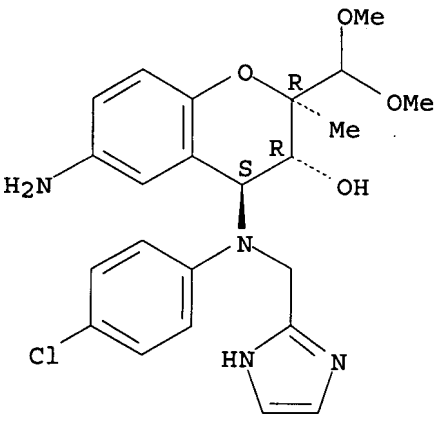
L8   ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2006:1199201  HCAPLUS
DOCUMENT NUMBER:         146:19691
TITLE:                   KR-31831, a new synthetic anti-ischemic agent,
                         inhibits in vivo and in vitro angiogenesis
AUTHOR(S):               Yi, Eui-Yeun; Park, Shi Young; Song, Hyun Seok; Son,
                         Myung Jin; Yi, Kyu-Yang; Yoo, Sung-En; Kim, Yung-Jin
```

CORPORATE SOURCE: Department of Molecular Biology, Pusan National University, Pusan, 609-735, S. Korea
SOURCE: Experimental and Molecular Medicine (2006), 38(5), 502-508
CODEN: EMMEF3; ISSN: 1226-3613
PUBLISHER: Korean Society of Medical Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Angiogenesis is considered to be an integral process to the growth and spread of solid tumors. Anti-angiogenesis therapy recently was found to be 1 of the most promising anti-cancer therapeutic strategies. In this study, we provide several lines of evidences showing that KR-31831, a new benzopyran derivative, has anti-angiogenic activities. KR-31831 inhibited the proliferation, migration, invasion and tube formation of bovine aortic endothelial cells (BAECs), and suppressed the release of matrix metalloproteinase-2 (MMP-2) of BAECs. KR-31831 also inhibited in vivo angiogenesis in mouse Matrigel plug assay. Furthermore, the mRNA expressions of basic fibroblast growth factor (bFGF), fibroblast growth factor receptor-2 (FGFR-2), and vascular endothelial growth factor receptor-2 (VEGFR-2) were decreased by KR-31831. Taken together, these results suggest that KR-31831 acts as a novel angiogenesis inhibitor and might be useful for treating hypervascularized cancers.

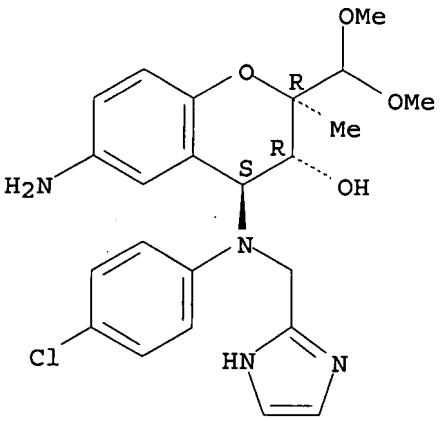
IT 571141-49-6, KR-31831
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(KR-31831 inhibits in vivo and in vitro angiogenesis)
RN 571141-49-6 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-(CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:146422 HCAPLUS
DOCUMENT NUMBER: 144:183984
TITLE: Characterization of cytochrome P450 enzymes and P-glycoprotein involved in the metabolism and transport of a new anti-angiogenic agent KR-31831



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

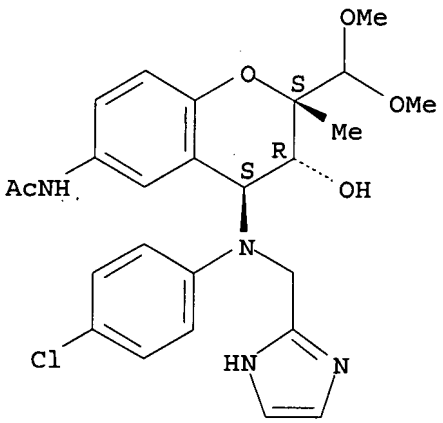
L8 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1082825 HCAPLUS
DOCUMENT NUMBER: 143:452120
TITLE: Metabolism of a novel antiangiogenic agent KR-31831 in rats using liquid chromatography-electrospray mass spectrometry
AUTHOR(S): Kim, Hui-Hyun; Paek, In Bok; Ji, Hye Young; Lee, Sunkyung; Yi, Kyu Yang; Lee, Hye Suk
CORPORATE SOURCE: Drug Metabolism and Bioanalysis Laboratory, College of Pharmacy and Phytofermantation Research Center, Wonkwang University, Iksan, S. Korea
SOURCE: Journal of Separation Science (2005), 28(14), 1818-1822
CODEN: JSSCCJ; ISSN: 1615-9306
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English

AB KR-31831 ((2S,3R,4S)-4-(((1H-imidazol-2-yl)methyl)(4-chlorophenyl)amino)-6-amino-2-(dimethoxymethyl)-2-methyl-3,4-dihydro-2H-chromen-3-ol) is a novel antiangiogenic agent. In vitro and in vivo metabolism of KR-31831 in rats has been investigated using LC-MS and LC-MS/MS anal. Incubation of rat liver microsomes and hepatocytes with KR-31831 produced three metabolites (M1-M3). M1, M2, and M3 were identified as N-((1H-imidazol-2-yl)methyl)-4-chlorobenzenamine, (2R,3R,4S)-4-(((1H-imidazol-2-yl)methyl)(4-chlorophenyl)amino)-6-amino-2-(hydroxymethyl)-2-methyl-3,4-dihydro-2H-chromen-3-ol, and N-((2S,3R,4S)-4-(((1H-imidazol-2-yl)methyl)(4-chlorophenyl)amino)-2-(dimethoxymethyl)-3-hydroxy-2-methyl-3,4-dihydro-2H-chromen-6-yl)acetamide, resp., by co-chromatog. with the authentic stds. and by comparison with product ion spectra of the authentic stds. Those in vitro metabolites were also detected in bile, plasma, or urine samples after an i.v. administration of KR-31831 to rats. The metabolic routes for KR-31381 included the metabolism of acetal group to hydroxymethyl group (M2), N-dealkylation to M1, and N-acetylation at the 6-amino group (M3).

IT 869116-59-6
RL: ANT (Analyte); ANST (Analytical study)
(metabolism of a novel antiangiogenic agent KR-31831 in rats using liquid chromatog.-electrospray mass spectrometry)
RN 869116-59-6 HCAPLUS
CN Acetamide, N-[(2S,3R,4S)-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-

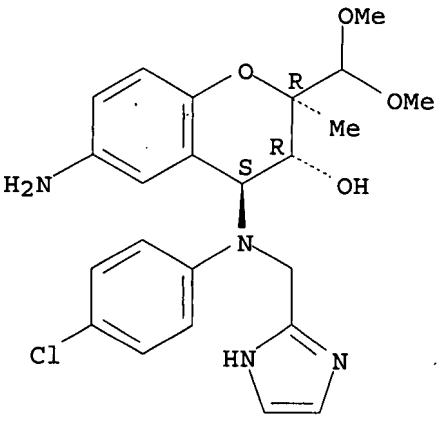
2-(dimethoxymethyl)-3,4-dihydro-3-hydroxy-2-methyl-2H-1-benzopyran-6-yl]-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 571141-49-6, KR 31831
RL: ANT (Analyte); PKT (Pharmacokinetics); ANST (Analytical study); BIOL (Biological study)
(metabolism of a novel antiangiogenic agent KR-31831 in rats using liquid chromatog.-electrospray mass spectrometry)
RN 571141-49-6 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-
(CA INDEX NAME)

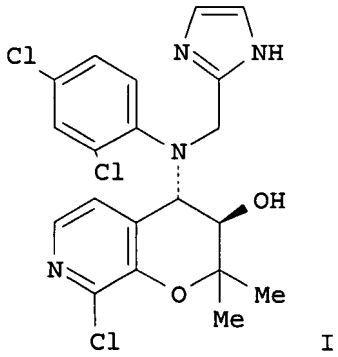
Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:452927 HCAPLUS
DOCUMENT NUMBER: 144:232975
TITLE: 4-[(N-imidazol-2-ylmethyl)anilino]pyranopyridine analogs as novel anti-angiogenic agents
AUTHOR(S): Lee, Sunkyung; Chae, Sun Mi; Yi, Kyu Yang; Kim,

Nakjeong; Oh, Chang Ho
CORPORATE SOURCE: Medicinal Science Division, Korea Research Institute of Chemical Technology, Daejeon, 305-600, S. Korea
SOURCE: Bulletin of the Korean Chemical Society (2005), 26(4), 619-628
CODEN: BKCSDE; ISSN: 0253-2964
PUBLISHER: Korean Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:232975
GI



I

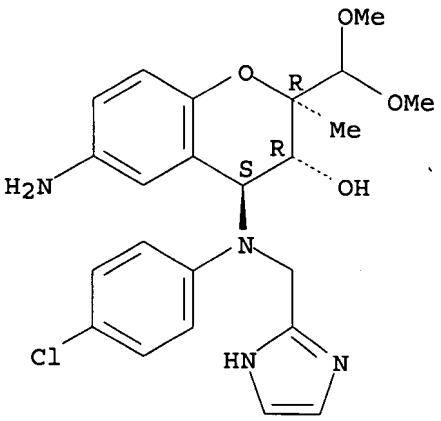
AB Replacement of the benzopyran ring with pyranopyridines was accomplished for 4-[(N-imidazol-2-ylmethyl)-4-chloroanilino]benzopyran, previously discovered as anti-angiogenic agent with antitumor activity. The [3,2-c]-, [3,2-b]-, [2,3-c]-, and [2,3-b]-pyranopyridines with N-(imidazol-2-ylmethyl)aniline moiety at the 4-position (e. g. I), were synthesized, and evaluated for primary anti-angiogenic properties through primary cultured HUVEC tube formation assay. The pyranopyridine ring, especially [3,2-b]- and [2,3-c]-isomer, can replace the benzopyran ring and can be optimized through the introduction of substituents both on the pyranopyridine ring and the aniline moiety for the identification of a novel anti-angiogenic agent.

IT 571141-49-6
RL: PAC (Pharmacological activity); BIOL (Biological study)
(preparation and angiogenesis inhibition by [(N-imidazolylmethyl)anilino]pyranopyridine isomers prepared via pyranopyridine epoxidn. followed by ring opening reactions with (imidazolylmethyl)anilines)

RN 571141-49-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-(CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:95257 HCAPLUS
DOCUMENT NUMBER: 142:309403
TITLE: Pharmacokinetics of a novel antiangiogenic agent KR-31831 in rats
AUTHOR(S): Kim, Sook J.; Lee, Hong I.; Ji, Hye Y.; Moon, Ya; Paek, In B.; Lee, Sunkyung; Yi, Kyu Y.; Yoo, Sun D.; Lee, Hye S.
CORPORATE SOURCE: Drug Metabolism and Bioanalysis Laboratory, College of Pharmacy, Wonkwang University, Iksan, 570-749, S. Korea
SOURCE: Biopharmaceutics & Drug Disposition (2005), 26(1), 21-26
CODEN: BDDID8; ISSN: 0142-2782
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study reports the absorption, dose-linearity and pharmacokinetics of a novel antiangiogenic agent KR-31831 in rats after i.v. and oral administration at doses of 5, 10 and 25 mg/kg on both occasions. Concns. of KR-31831 were determined by a validated LC/MS/MS assay method. After i.v. injection, plasma concentration-time profiles showed multi-compartmental characteristics, and there were no significant differences in Cl (20.8-27.7 mL/min/kg) and dose-normalized AUC (178.1-231 μg · min/mL based on the 5 mg/kg dose) as a function of dose. However, Vss was significantly increased at the 25 mg/kg dose (4931 mL/kg) compared with those (2288-2421 mL/kg) at lower doses. Subsequently, t1/2 was increased from 143-159 min at the lower doses to 304 min at the 25 mg/kg dose. The altered VSS was found to be a result of reduced plasma protein binding at relatively high concns. Following oral administration (doses 5-25 mg/kg), the absolute oral bioavailability ranged from 37.8% to 46.3%, and there were no significant alterations in dose-normalized AUC, Tmax, Cmax and t1/2 as a function of dose. The extent of urinary excretion was low for both i.v. (0.35%-0.54%) and oral (0.13%-0.33%) doses. Further discussions on the chemical and microsomal stability were included. In conclusion, dose-independent absorption kinetics were observed at oral doses from 5 to 25 mg/kg in rats. Orally administered KR-31831 could be eliminated mainly by the liver metabolic pathway.

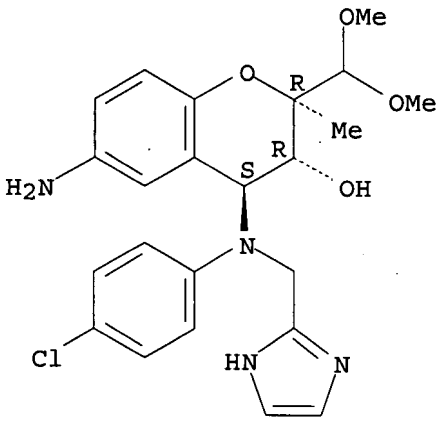
IT 571141-49-6, KR-31831

RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics of antiangiogenic agent KR-31831 in rats)

RN 571141-49-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-(CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:143140 HCAPLUS

DOCUMENT NUMBER: 140:181449

TITLE: Preparation of imidazolylmethylaminobenzopyrans as antiangiogenic agents

INVENTOR(S): Yi, Kyu Yang; Lee, Sun Kyung; Yoo, Sung-eun; Suh, Jee Hee; Kim, Nak-Jeong; Hwang, Sun Kyung; Lee, Byung-ho; Seo, Ho Won; Lee, Chong Ock; Choi, Sang-un

PATENT ASSIGNEE(S): Korea Research Institute of Chemical Technology, S. Korea

SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014898	A1	20040219	WO 2003-KR1534	20030730

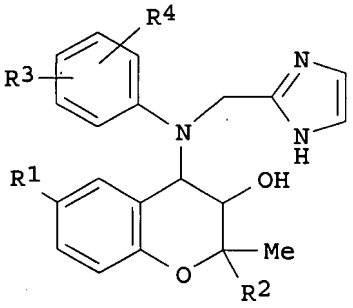
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

KR 2004014023	A	20040214	KR 2002-47189		20020809
CA 2493966	A1	20040219	CA 2003-2493966		20030730
AU 2003247213	A1	20040225	AU 2003-247213		20030730
EP 1546136	A1	20050629	EP 2003-784665		20030730
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
CN 1675202	A	20050928	CN 2003-819195		20030730
JP 2006509725	T	20060323	JP 2004-527422		20030730
US 2005267188	A1	20051201	US 2005-523015		20050202
PRIORITY APPLN. INFO.:			KR 2002-47189	A	20020809
			WO 2003-KR1534	W	20030730

OTHER SOURCE(S): CASREACT 140:181449; MARPAT 140:181449

GI



I

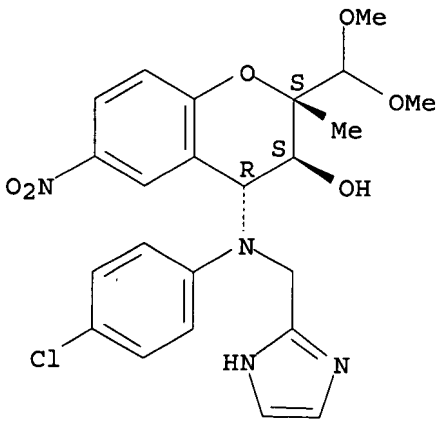
AB Imidazolylmethylaminobenzopyrans I [R1 = H, CN, NO2, NH2; R2 = dialkoxymethyl, alkylenedioxymethyl; R3, R4 = H, Cl, Br, F, alkyl, CF3, OCF3, NO2, (un)substituted OH, CO2H] were prepared for use in the treatment of cancer, rheumatoid arthritis, and diabetic retinopathies through anti-angiogenic properties, and in the protection of heart and neuronal cells against ischemia-reperfusion injury or preserving organs. Thus, (2S,3R,4R)-3,4-dihydro-2-dimethoxymethyl-3,4-epoxy-2-methyl-6-nitro-2H-1-benzopyran was treated with N-(4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)amine to give (2S,3R,4R)-I [R1 = NO2, R2 = CH(OMe)2, R3 = 4-Cl, R4 = H] which showed strong inhibition of HUVEC tube formation at 10 μM.

IT 571141-37-2P 571141-39-4P 660404-73-9P
660404-74-0P 660404-75-1P 660404-76-2P
660404-77-3P 660404-78-4P 660404-80-8P
660404-81-9P 660404-82-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of imidazolylmethylaminobenzopyrans as antiangiogenic agents)

RN 571141-37-2 HCAPLUS

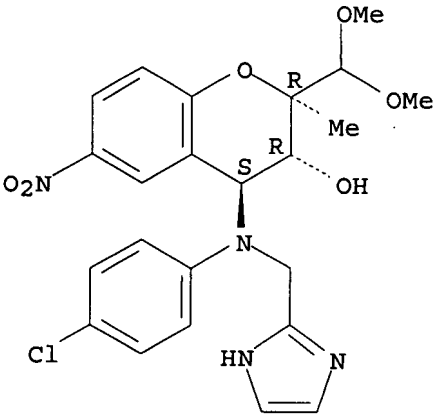
CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



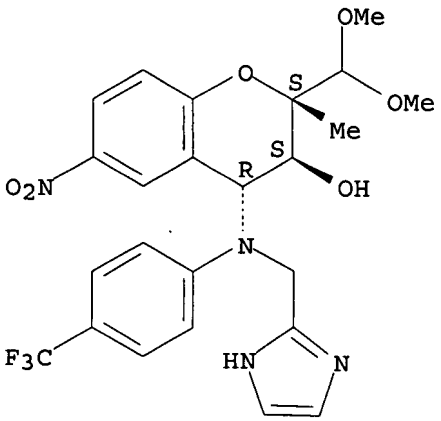
RN 571141-39-4 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



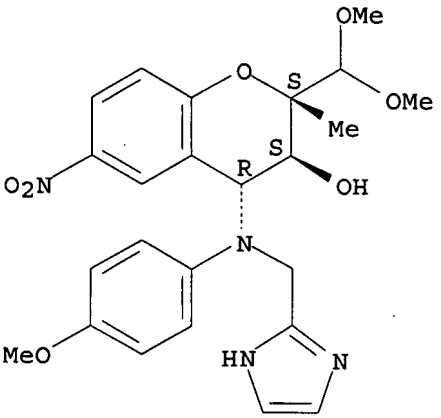
RN 660404-73-9 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethyl)phenyl]amino]-2-methyl-6-nitro-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



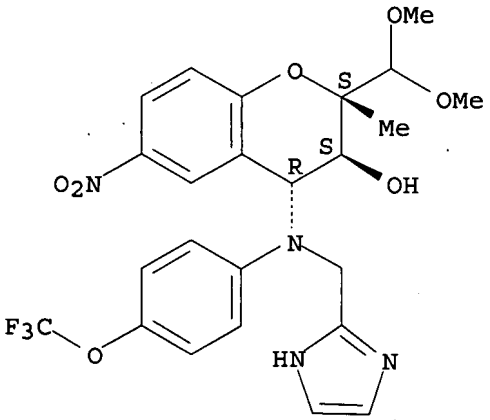
RN 660404-74-0 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



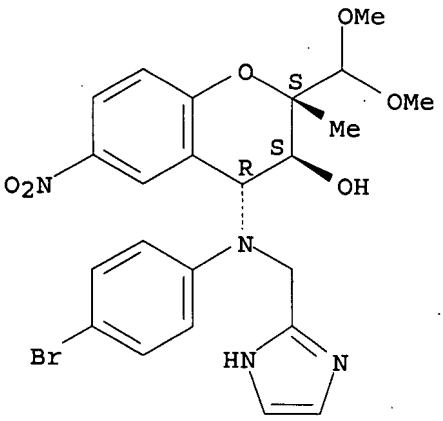
RN 660404-75-1 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethoxy)phenyl]amino]-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



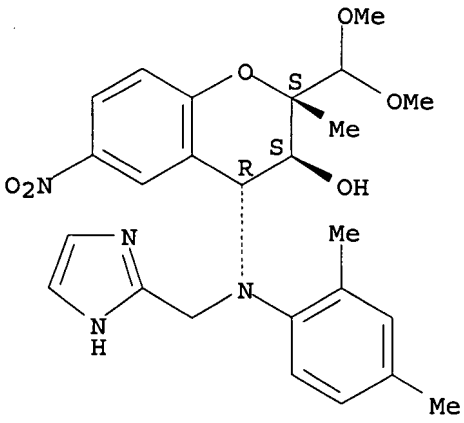
RN 660404-76-2 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 4-[(4-bromophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



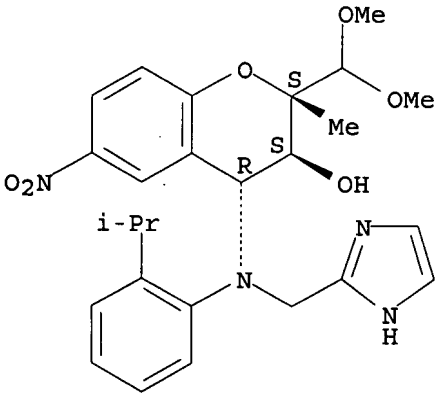
RN 660404-77-3 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-4-[(2,4-dimethylphenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



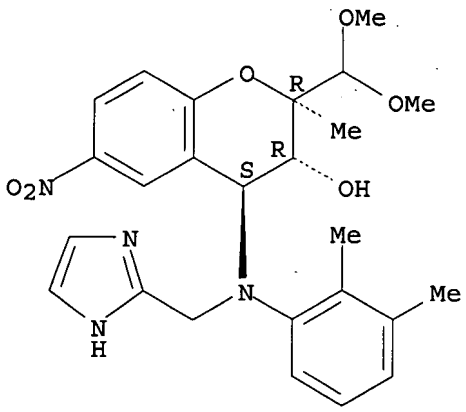
RN 660404-78-4 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[2-(1-methylethyl)phenyl]amino]-2-methyl-6-nitro-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



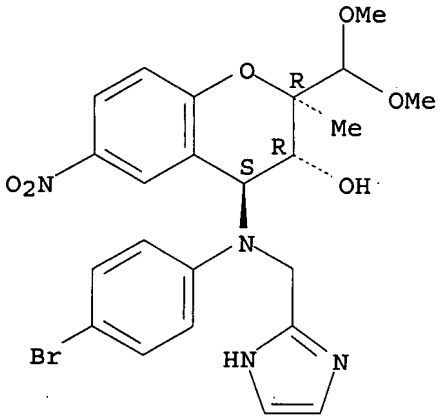
RN 660404-80-8 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-4-[(2,3-dimethylphenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-6-nitro-, (2R,3R,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



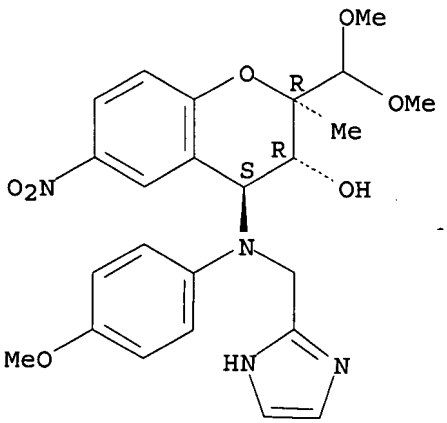
RN 660404-81-9 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 4-[(4-bromophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 660404-82-0 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

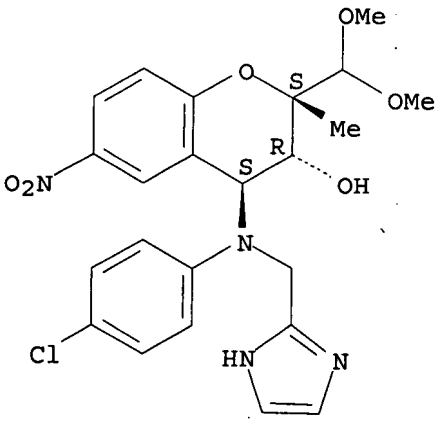


IT 571141-36-1P 571141-38-3P 571141-47-4P
571141-49-6P 660404-90-0P 660404-91-1P
660404-92-2P 660404-93-3P 660404-94-4P
660404-95-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of imidazolylmethylaminobenzopyrans as antiangiogenic agents)

RN 571141-36-1 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3R,4S)- (9CI) (CA INDEX NAME)

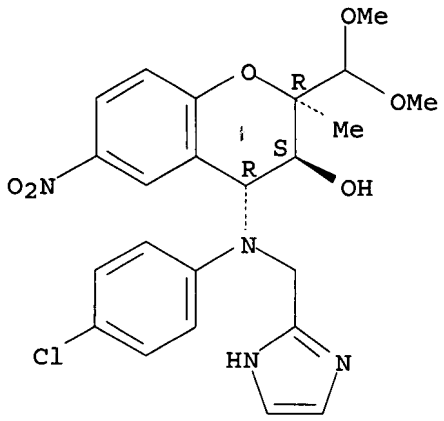
Absolute stereochemistry.



RN 571141-38-3 HCAPLUS

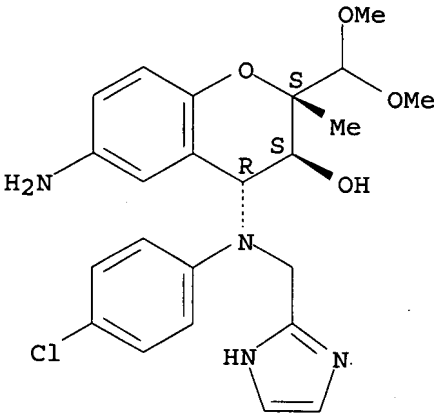
CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



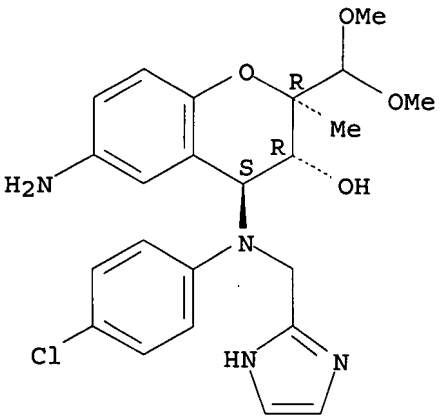
RN 571141-47-4 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



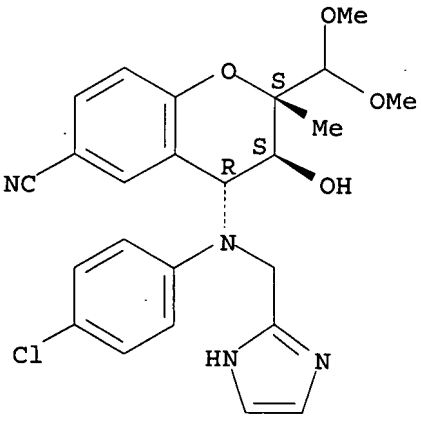
RN 571141-49-6 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-(CA INDEX NAME)

Absolute stereochemistry.



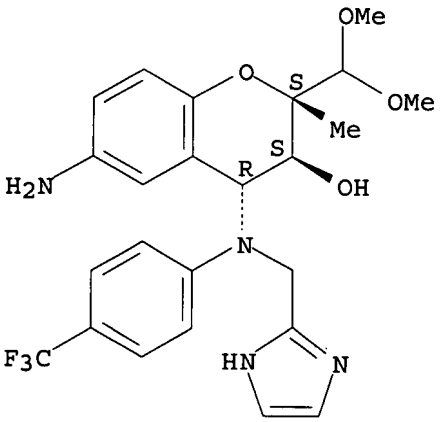
RN 660404-90-0 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-3-hydroxy-2-methyl-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



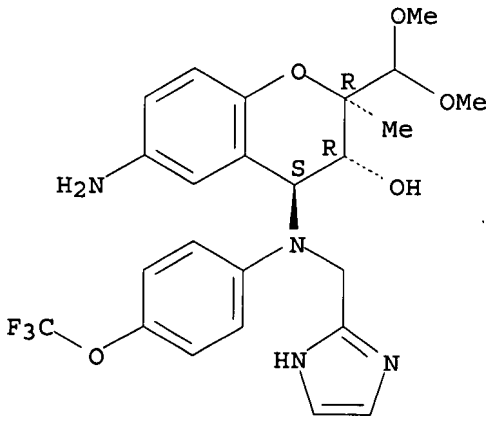
RN 660404-91-1 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethyl)phenyl]amino]-2-methyl-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



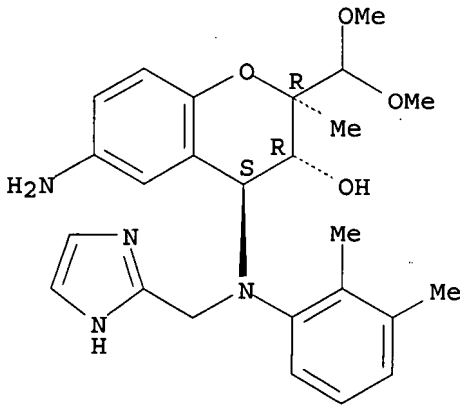
RN 660404-92-2 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethoxy)phenyl]amino]-2-methyl-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



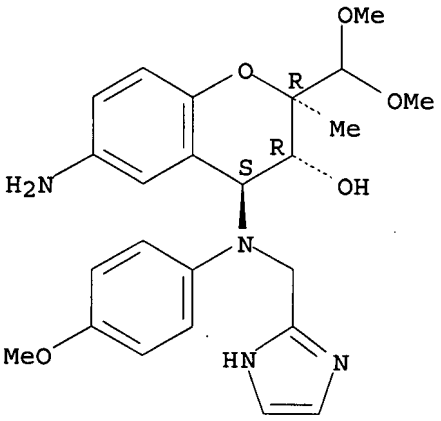
RN 660404-93-3 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-4-[(2,3-dimethylphenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



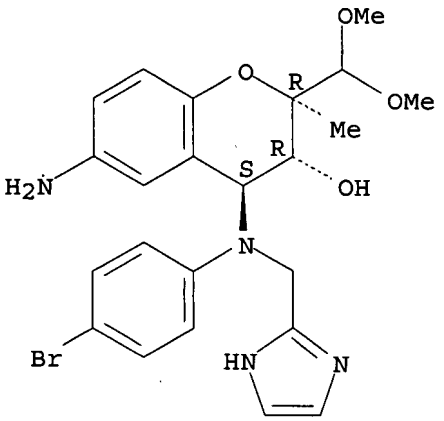
RN 660404-94-4 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 660404-95-5 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-bromophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

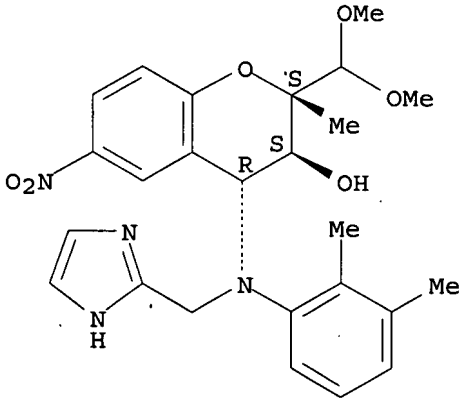


IT 660404-79-5P 660404-83-1P 660404-84-2P
660404-89-7P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of imidazolylmethylaminobenzopyrans as antiangiogenic agents)

RN 660404-79-5 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-4-[(2,3-dimethylphenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

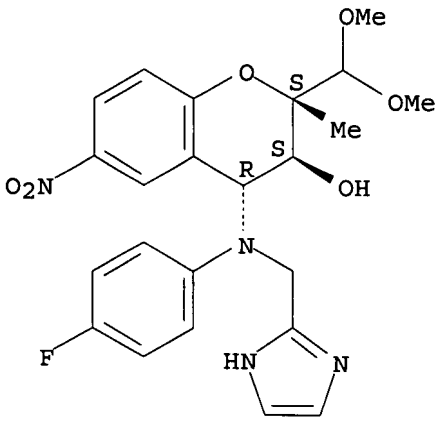
Absolute stereochemistry.



RN 660404-83-1 HCAPLUS

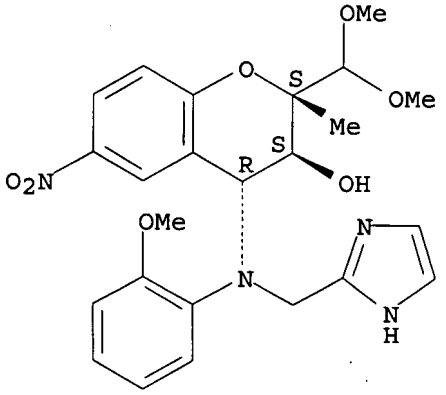
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



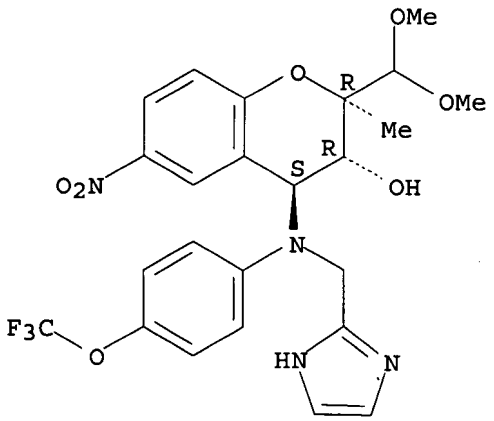
RN 660404-84-2 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(2-methoxyphenyl)amino]-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 660404-89-7 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethoxy)phenyl]amino]-2-methyl-6-nitro-, (2R,3R,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

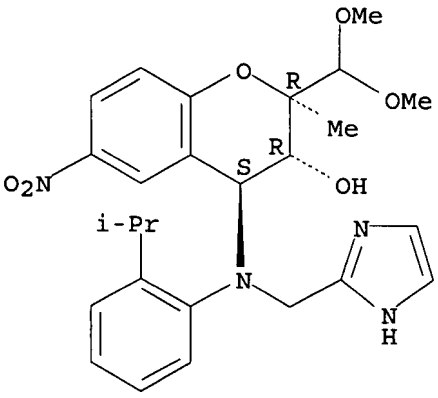


IT 660404-85-3P 660404-86-4P 660404-87-5P
660404-88-6P 660404-96-6P 660404-97-7P
660404-98-8P 660404-99-9P 660405-00-5P
660405-01-6P 660405-02-7P 660405-03-8P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of imidazolylmethylaminobenzopyrans as antiangiogenic agents)

RN 660404-85-3 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[2-(1-methylethyl)phenyl]amino]-2-methyl-6-nitro-, (2R,3R,4S)-(9CI) (CA INDEX NAME)

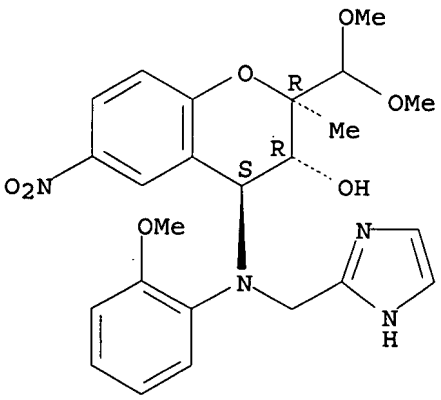
Absolute stereochemistry.



RN 660404-86-4 HCAPLUS

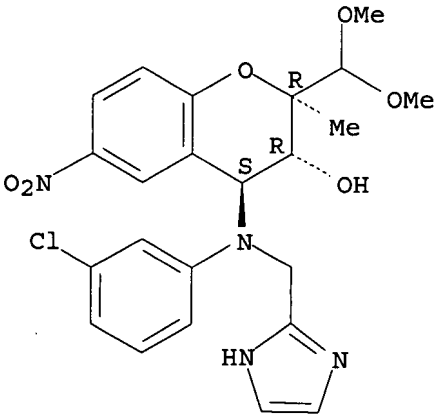
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(2-methoxyphenyl)amino]-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



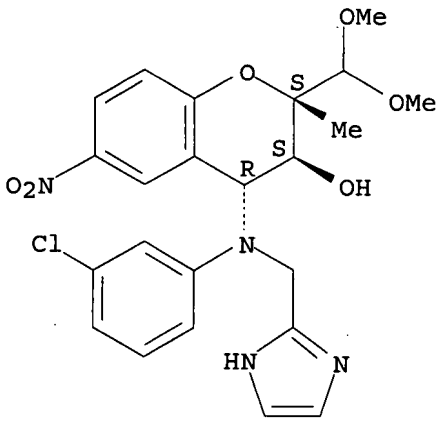
RN 660404-87-5 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 4-[(3-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



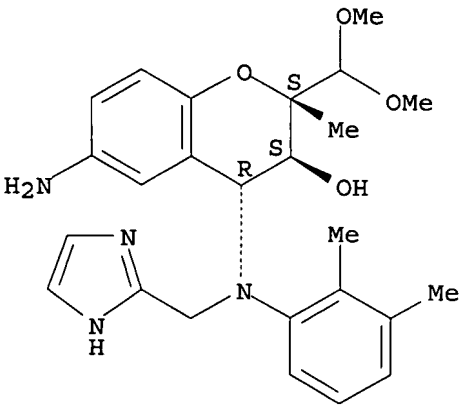
RN 660404-88-6 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 4-[(3-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



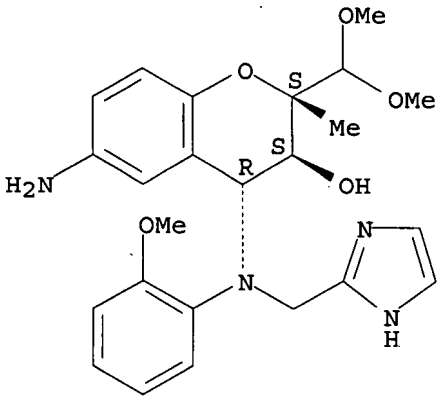
RN 660404-96-6 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-4-[(2,3-dimethylphenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



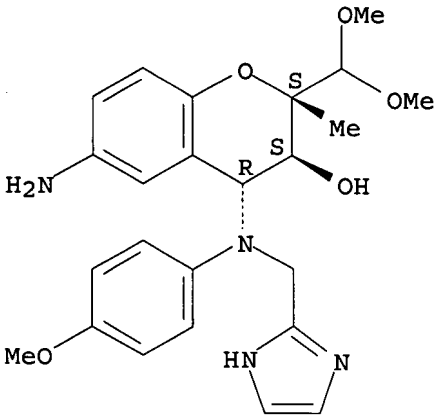
RN 660404-97-7 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(2-methoxyphenyl)amino]-2-methyl-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



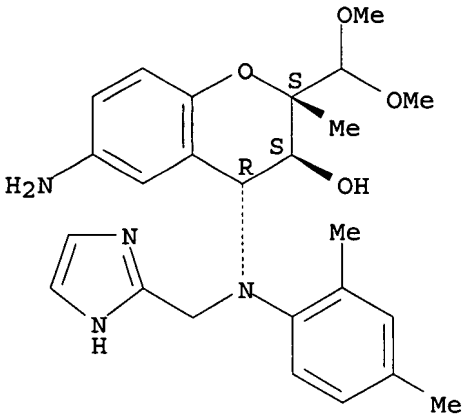
RN 660404-98-8 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



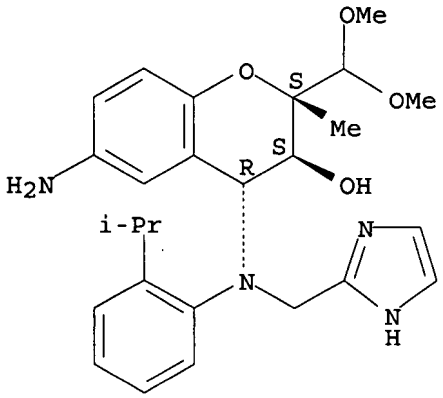
RN 660404-99-9 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-4-[(2,4-dimethylphenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



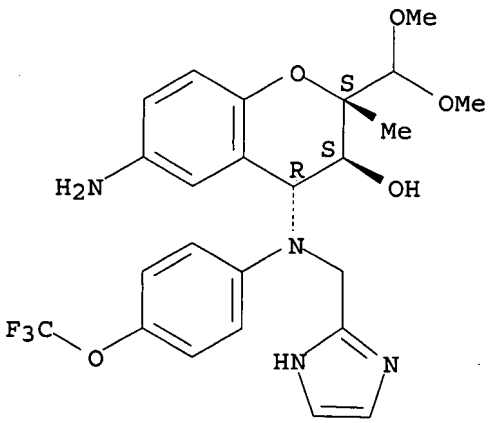
RN 660405-00-5 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[2-(1-methylethyl)phenyl]amino]-2-methyl-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



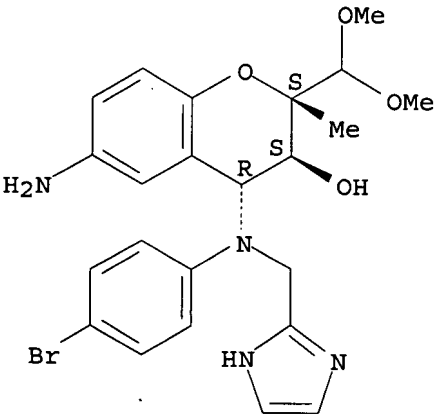
RN 660405-01-6 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethoxy)phenyl]amino]-2-methyl-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



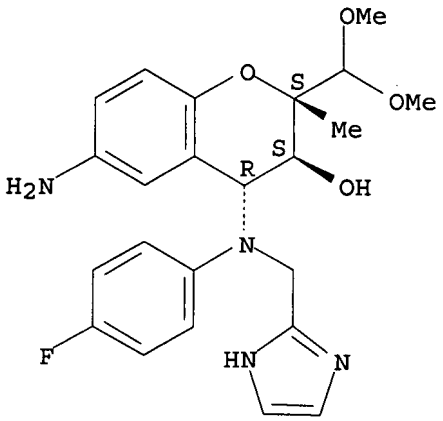
RN 660405-02-7 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-bromophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 660405-03-8 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

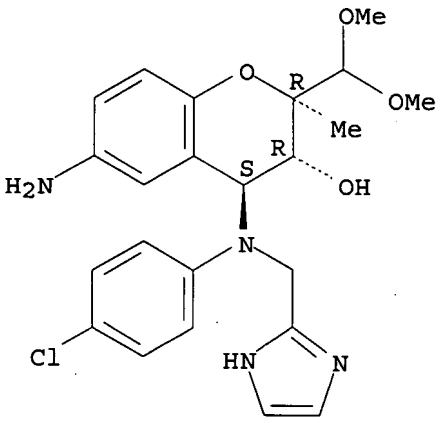
L8 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:131575 HCAPLUS
DOCUMENT NUMBER: 141:81619
TITLE: Determination of a Novel Antiangiogenic Agent KR-31831 in Rat Plasma by Liquid Chromatography-Tandem Mass Spectrometry
AUTHOR(S): Kim, Sook Jin; Lee, Seung-Seok; Ji, Hye Young; Lee, Hong Il; Lee, Seonkyoung; Li, Kyu Yang; Yoo, Seong Eun; Hwang, Jeongsug; Lee, Hye-Suk
CORPORATE SOURCE: College of Pharmacy, Drug Metabolism and Bioanalysis Laboratory, Wonkwang University, Iksan, S. Korea
SOURCE: Analytical Letters (2004), 37(2), 283-292
CODEN: ANALBP; ISSN: 0003-2719
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A liquid chromatog.-tandem mass spectrometric (LC/MS/MS) method was developed for the determination of a new anti-angiogenic drug KR-31831 in rat plasma. KR-31831 and internal standard, KR-31543 were extracted from rat plasma with CH2Cl2 at basic pH. A reverse-phase LC separation was performed on Luna C8 column with the mixture of MeCN-ammonium formate (10 mM, pH 4.5) (67:33, volume/volume) as mobile phase. The detection of analytes was performed using an electrospray ionization tandem mass spectrometry in the multiple-reaction-monitoring mode. The standard curve was linear (r = 0.999) over the concentration range of 1.0-500 ng/mL. The coefficient of variation of intra- and inter-assay ranged from 0.8-3.9% and 1.4-3.9%, resp. The recoveries of KR-31831 ranged from 80.9% to 86.7%, with that of KR-31543 (internal standard) being 99.2 ± 2.7%. The lower limits of quantification for KR-31831 was 1.0 ng/mL using 100 μL plasma sample. This method was applied to the pharmacokinetic study of KR-31831 in rats.

IT 571141-49-6, KR 31831
RL: ANT (Analyte); PKT (Pharmacokinetics); ANST (Analytical study); BIOL (Biological study)
(determination of a novel antiangiogenic agent KR-31831 in rat plasma by liquid chromatog.-tandem mass spectrometry)
RN 571141-49-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-(CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

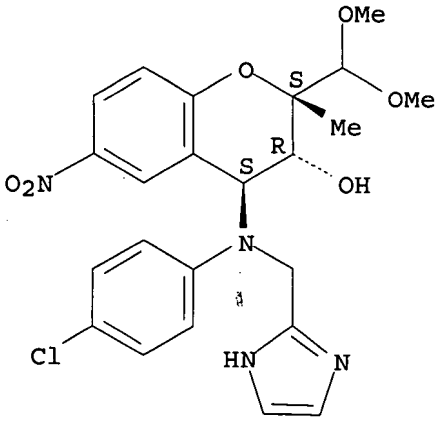
L8 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:326008 HCAPLUS
DOCUMENT NUMBER: 139:143352
TITLE: Identification of a novel antiangiogenic agent; 4-(N-Imidazol-2-ylmethyl)amino-benzopyran analogues
AUTHOR(S): Kim, Nakjeong; Lee, Sunkyung; Yi, Kyu Yang; Yoo, Sung-eun; Kim, Guncheol; Lee, Chong-Ock; Park, Sung Hee; Lee, Byung Ho
CORPORATE SOURCE: Medicinal Science Division, Korea Research Institute of Chemical Technology, Yoosung-gu, Taejon, 305-600, S. Korea
SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(10), 1661-1663
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:143352

AB A series of 4-(N-imidazol-2-ylmethyl)aminobenzopyran analogs, originally designed as KATP openers for ischemic diseases, showed antiangiogenic properties through the inhibition of HUVEC tube formation. Especially one of p-Cl substituted analogs completely inhibited HUVEC tube formation at 10 μM and significantly inhibited tumor growth by 52% on A549 (human non small cell lung carcinoma) in nude mice xenografts without any significant side effects.

IT 571141-36-1P 571141-37-2P 571141-38-3P
571141-39-4P 571141-40-7P 571141-41-8P
571141-42-9P 571141-43-0P 571141-44-1P
571141-45-2P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(identification of a novel antiangiogenic agent and structure-activity relationship 4-(N-imidazol-2-ylmethyl)amino benzopyran analogs)

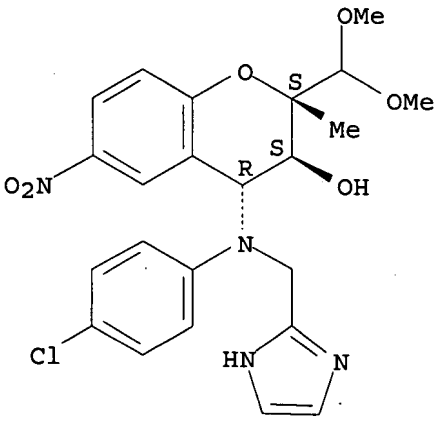
RN 571141-36-1 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



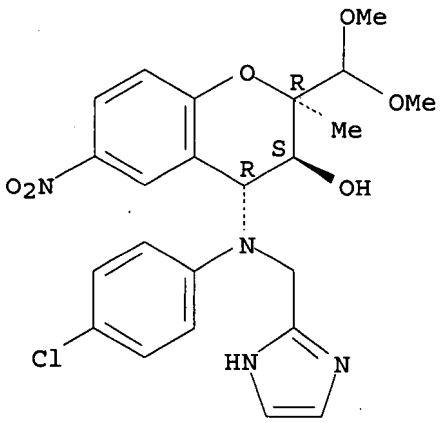
RN 571141-37-2 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



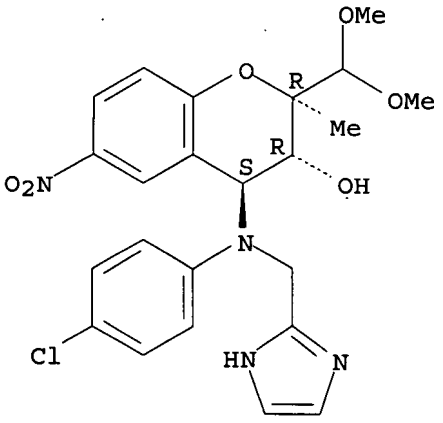
RN 571141-38-3 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



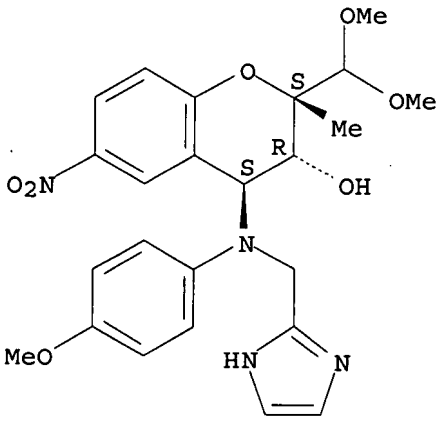
RN 571141-39-4 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



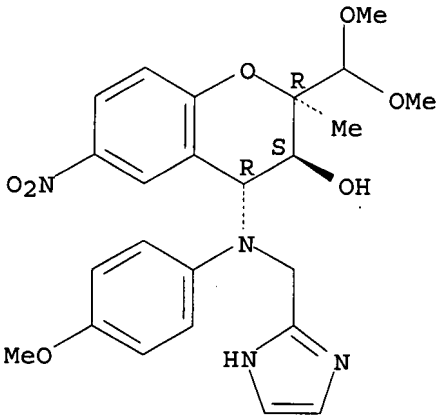
RN 571141-40-7 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-6-nitro-, (2S,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



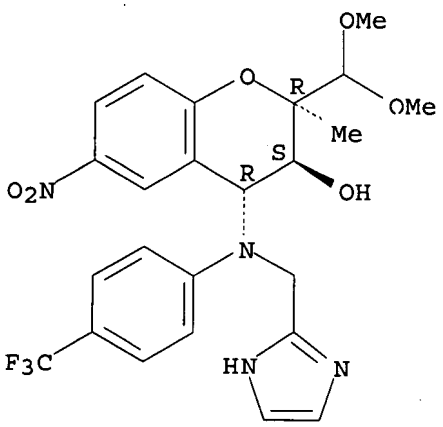
RN 571141-41-8 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-6-nitro-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



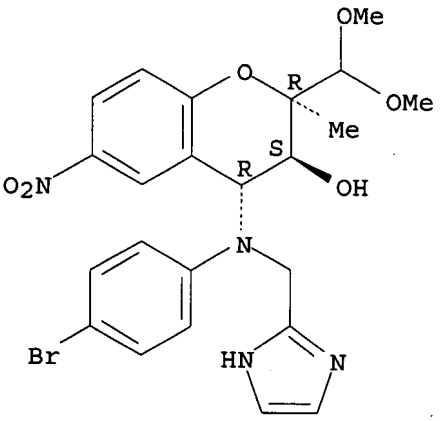
RN 571141-42-9 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethyl)phenyl]amino]-2-methyl-6-nitro-, (2R,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



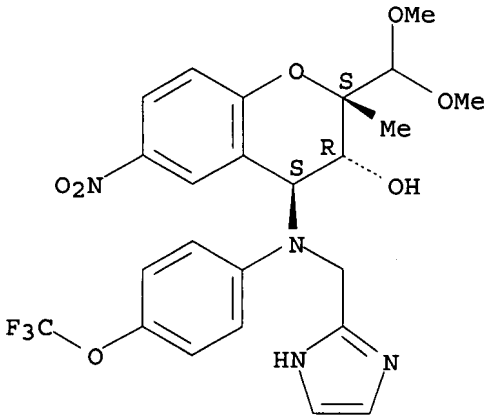
RN 571141-43-0 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 4-[(4-bromophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



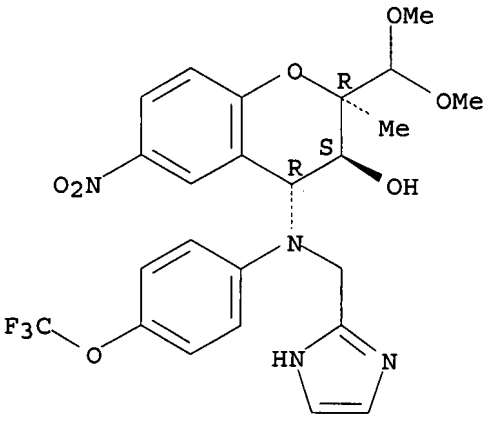
RN 571141-44-1 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethoxy)phenyl]amino]-2-methyl-6-nitro-, (2S,3R,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



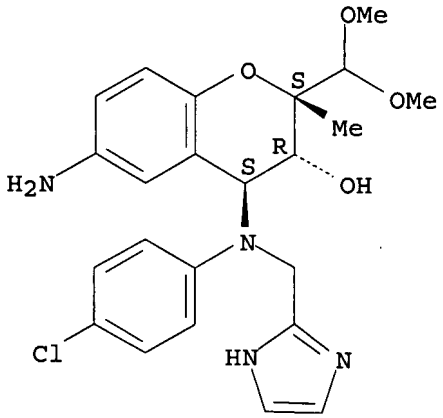
RN 571141-45-2 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethoxy)phenyl]amino]-2-methyl-6-nitro-, (2R,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



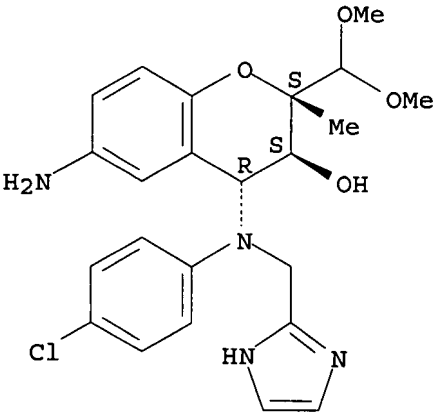
IT 571141-46-3P 571141-47-4P 571141-48-5P
571141-49-6P 571141-50-9P 571141-51-0P
571141-52-1P 571141-53-2P 571141-54-3P
571141-55-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(identification of a novel antiangiogenic agent and structure-activity relationship 4-(N-imidazol-2-ylmethyl)amino benzopyran analogs)
RN 571141-46-3 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2S,3R,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



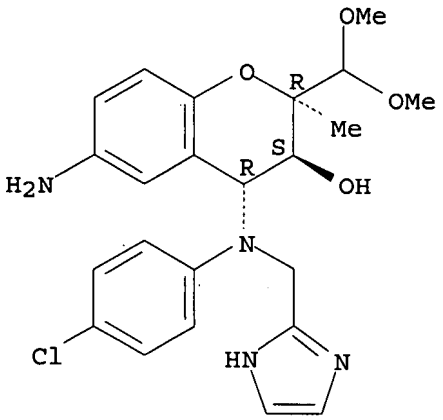
RN 571141-47-4 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



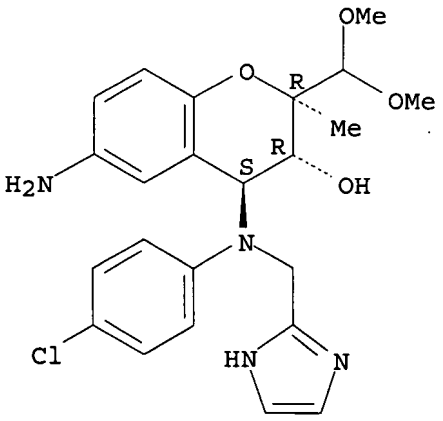
RN 571141-48-5 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



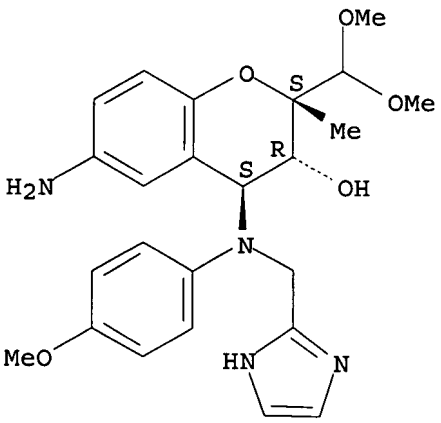
RN 571141-49-6 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-(CA INDEX NAME)

Absolute stereochemistry.



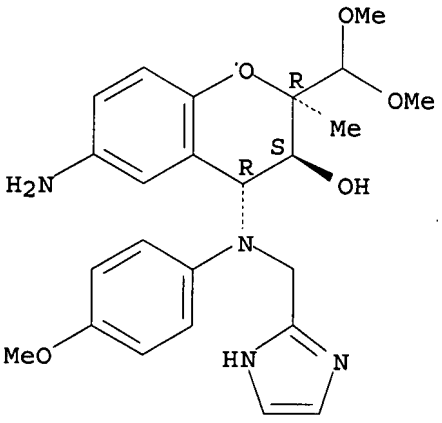
RN 571141-50-9 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-, (2S,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



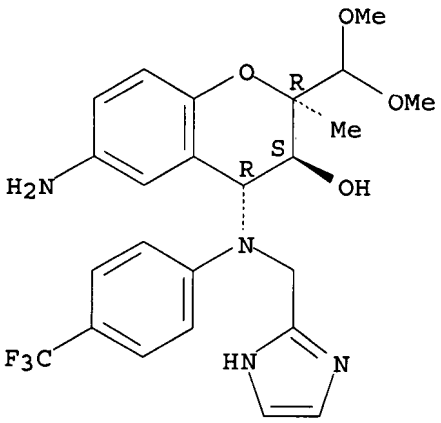
RN 571141-51-0 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



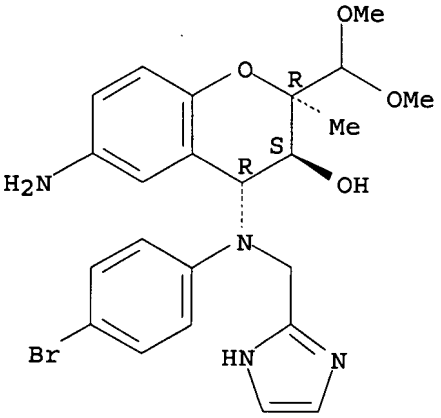
RN 571141-52-1 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethyl)phenyl]amino]-2-methyl-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



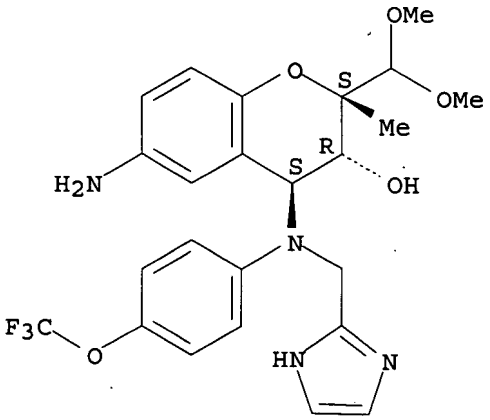
RN 571141-53-2 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-bromophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



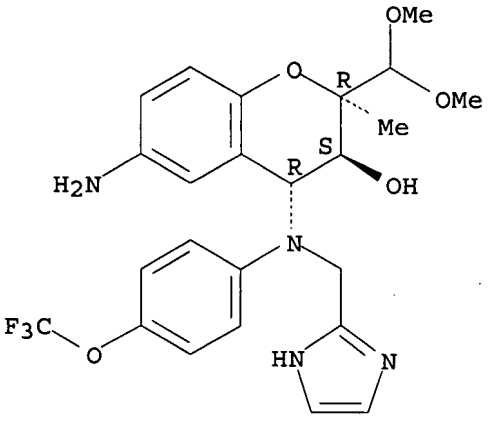
RN 571141-54-3 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethoxy)phenyl]amino]-2-methyl-, (2S,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 571141-55-4 HCAPLUS
CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethoxy)phenyl]amino]-2-methyl-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l9 ibib abs hitstr tot

L9 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:845162 HCAPLUS
DOCUMENT NUMBER: 139:576
TITLE: Pharmacologic profile of the selective mitochondrial-KATP opener BMS-191095 for treatment of acute myocardial ischemia
AUTHOR(S): Grover, Gary J.; Atwal, Karnail S.
CORPORATE SOURCE: Cardiovascular and Metabolic Diseases Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Pennington, NJ, USA
SOURCE: Cardiovascular Drug Reviews (2002), 20(2), 121-136

CODEN: CDREEA; ISSN: 0897-5957
PUBLISHER: Neva Press
DOCUMENT TYPE: Journal
LANGUAGE: English

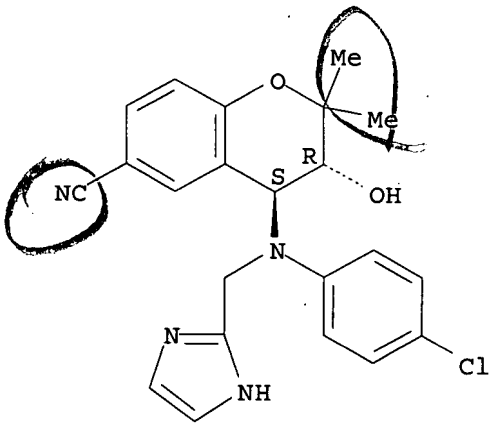
AB ATP-sensitive potassium channel (KATP) openers as a class protect ischemic myocardium. The protective effects are independent of vasodilator activity and effects on action potential shortening, actions typically associated with sarcolemmal KATP activation. BMS-191095 is a novel mitochondrial KATP opener which protects ischemic myocardium while having no electrophysiol. or vasodilator effects (determined in vitro and in vivo). The cardioprotective effects were determined in isolated rat hearts subjected to ischemia and reperfusion. Protective effects were deduced from increased time to contracture formation during ischemia, improved reperfusion recovery of contractile function, and reduced reperfusion lactate dehydrogenase release. The cardioprotective effects of BMS-191095 were observed at concns. at which this compound selectively opened cardiac mitochondrial KATP channels. This effect was consistent with the pharmacol. profile of this agent. The protective effects were abolished by mitochondrial KATP inhibition. Unlike first-generation KATP openers, BMS-191095 is expected to protect ischemic myocardium with little hemodynamic sequelae and without any proarrhythmic potential. BMS-191095 is potentially useful clin. as a cardioprotective agent. It is also a useful tool for basic research.

IT 166095-21-2, BMS-191095
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)
(mitochondrial-KATP opener BMS-191095 pharmacol. profile for treatment of acute myocardial ischemia)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:749914 HCAPLUS
DOCUMENT NUMBER: 138:297322
TITLE: In vivo characterization of the mitochondrial selective KATP opener (3R)-trans-4-((4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)dimethyl)-2H-1-benzopyran-6-

carbonitrile monohydrochloride (BMS-191095): cardioprotective, hemodynamic, and electrophysiological effects

AUTHOR(S): Grover, Gary J.; D'Alonzo, Albert J.; Darbenzio, Raymond B.; Parham, Charles S.; Hess, Thomas A.; Bathala, Mohinder S.

CORPORATE SOURCE: Metabolic and Cardiovascular Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Pennington, NJ, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2002), 303(1), 132-140
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

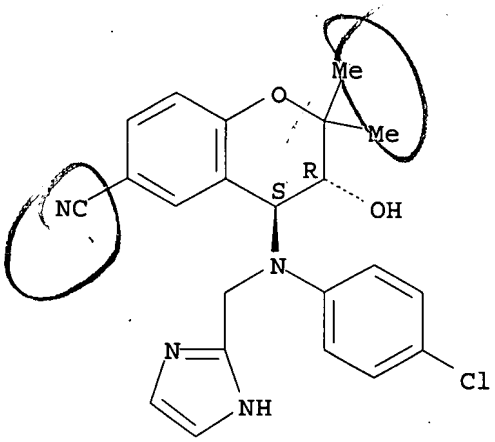
AB Recent studies have shown the importance of mitochondrial ATP-sensitive potassium channels (KATP) in cardioprotection, and studies in vitro have shown that the benzopyran analog BMS-191095 is a selective mitochondrial KATP opener with cardioprotective activity. The goal of this study was to show selective cardioprotection for BMS-191095 in vivo without hemodynamic or cardiac electrophysiol. effects expected for nonselective KATP openers. BMS-191095 reduced infarct size in anesthetized dogs (90-min ischemia + 5-h reperfusion) in a dose-dependent manner (ED25 = 0.4 mg/kg i.v.) with efficacious plasma concns. of 0.3 to 1.0 μM, which were consistent with potency in vitro. None of the doses of BMS-191095 tested caused any effect on peripheral or coronary hemodynamic status. Further studies in dogs showed no effects of BMS-191095 on cardiac conduction or action potential configuration within the cardioprotective dose range. In a programmed elec. stimulation model, BMS-191095 showed no proarrhythmic effects, which is consistent with its lack of effects on cardiac electrophysiol. status. BMS-191095 is a potent and efficacious cardioprotectant that is devoid of hemodynamic and cardiac electrophysiol. side effects of first generation KATP openers, which open both sarcolemmal and mitochondrial KATP. Selective opening or activation of mitochondrial KATP seems to be a potentially effective strategy for developing well tolerated and efficacious KATP openers.

IT 166095-21-2, BMS-191095
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vivo characterization of mitochondrial selective KATP opener BMS-191095 in relation to cardioprotective, hemodynamic, and electrophysiol. effects)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:293433 HCAPLUS
DOCUMENT NUMBER: 136:304080
TITLE: Diazoxide, pinacidil, nicorandil and/or BMS 191095 for treatment of apoptotic cell death in cardiac and neuronal cells
INVENTOR(S): Marban, Eduardo; O'Rourke, Brian; Akao, Massaharu; Ohler, Andreas
PATENT ASSIGNEE(S): Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002030411	A2	20020418	WO 2001-US31992	20011015 <--
WO 2002030411	A8	20020711		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002013174	A5	20020422	AU 2002-13174	20011015 <--
US 2002091144	A1	20020711	US 2001-977558	20011015 <--
US 6521617	B2	20030218		

PRIORITY APPLN. INFO.: US 2000-240267P P 20001013
WO 2001-US31992 W 20011015

AB New methods are provided for treating against apoptotic cell death, including apoptotic cardiac and neuronal cells. Therapies of the invention includes administration of a mitochondrial oxidizer compound to a subject in need thereof, such as a subject suffering from or susceptible to stroke, heart attack, brain or spinal cord trauma, or chronic conditions that can resulting apoptotic cell death such as a

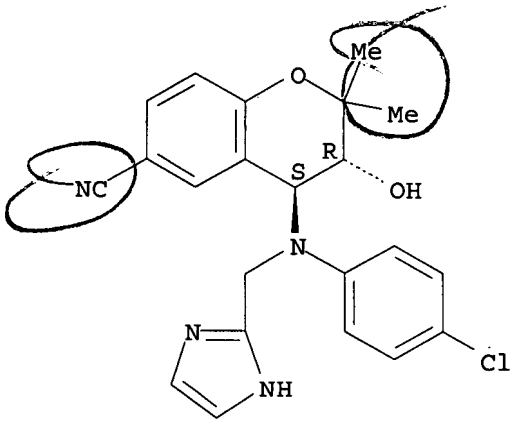
neurodegenerative disease and diabetes. Compds. used for treatment of apoptotic cell death included diazoxide, pinacidil, nicorandil, and/or BMS 191095.

IT 166095-21-2, BMS 191095
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diazoxide, pinacidil, nicorandil and/or BMS 191095 for treatment of apoptotic cell death in cardiac and neuronal cells)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:214387 HCAPLUS

DOCUMENT NUMBER: 137:72948

TITLE: Differential action of KR-31378, a novel potassium channel activator, on cardioprotective and hemodynamic effects

AUTHOR(S): Lee, Byung Ho; Seo, Ho Won; Yoo, Sung-Eun; Kim, Sun-Ok; Lim, Hong; Shin, Hwa Sup

CORPORATE SOURCE: Screening and Toxicology Research Center, Korea Research Institute of Chemical Technology, Taejon, 305-343, S. Korea

SOURCE: Drug Development Research (2001), 54(4), 182-190
CODEN: DDREDK; ISSN: 0272-4391

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The cardioprotective and hemodynamic effects of KR-31378, a highly cardioselective ATP-sensitive potassium channel activator with minimal hypotensive effect, were evaluated in rats and dogs, and compared with those of BMS-191095 and lemakalim. KR-31378 did not show any significant effect on methoxamine-induced aortic constriction up to doses of 300 μM, whereas BMS 191095 produced a moderately potent relaxant effect (IC50: 9.0 μM). In conscious rats, KR-31378 slightly increased blood pressure only at high dose (100 mg/kg, iv), unlike BMS-191095 that dose-dependently decreased blood pressure (ED20: 2.03 mg/kg). In anesthetized beagle dogs, KR-31378 was approx. 100-fold less potent than BMS-191095 for most hemodynamic parameters (iv ED20 for blood pressure

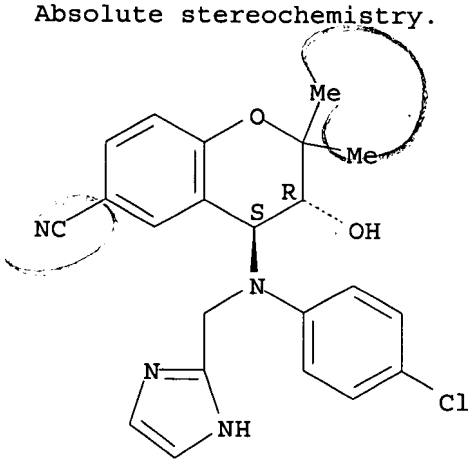
lowering: 33.7 and 0.37 mg/kg, resp.). In anesthetized rats subjected to 45-min coronary occlusion and 90-min reperfusion, KR-31378 (iv) dose-dependently reduced the infarct zone from 58.6% to 42.1%, 36.6%, and 34.3% for 0.1, 0.3, and 1.0 mg/kg, resp. ($P < 0.05$), the effects being comparable to those of BMS 191095. In anesthetized beagle dogs that underwent 2-h occlusion followed by 4.5-h reperfusion, KR-31378 (2 mg/kg, iv infusion) markedly reduced the infarct zone from 48.7% in controls to 19.1% at a dose of 2 mg/kg ($P < 0.05$). The reduction in infarct zone afforded by KR-31378 in rats was inhibited by pretreatment with selective ATP-sensitive potassium channel blockers, sodium 5-hydroxydecanoate and glibenclamide. These results indicate that KR-31378 is a potent cardioprotective agent with potentially minimal hypotensive effects. Thus, it could be potentially useful in the prevention and treatment of acute myocardial infarction.

IT 166095-21-2, BMS 191095
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differential action of KR-31378, a novel potassium channel activator, on cardioprotective and hemodynamic effects)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:380223 HCAPLUS

DOCUMENT NUMBER: 135:175010

TITLE: Pharmacologic characterization of BMS-191095, a mitochondrial KATP opener with no peripheral vasodilator or cardiac action potential shortening activity

AUTHOR(S): Grover, Gary J.; D'Alonzo, Albert J.; Garlid, Keith D.; Bajgar, Robert; Lodge, Nicholas J.; Sleph, Paul G.; Darbenzio, Raymond B.; Hess, Thomas A.; Smith, Mark A.; Paucek, Petr; Atwal, Karnail S.

CORPORATE SOURCE: Metabolic and Cardiovascular Diseases Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Pennington, NJ, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics

(2001), 297(3), 1184-1192
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

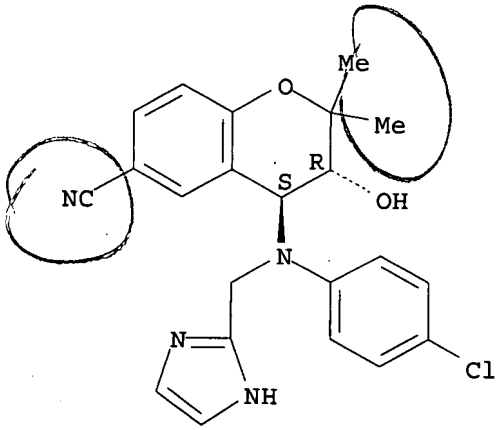
AB Previous work described ATP-sensitive K+ channel (KATP) openers (e.g., BMS-180448), which retain the cardioprotective activity of agents such as cromakalim while being significantly less potent as vasodilators. In this study, we describe the pharmacol. profile of BMS-191095, which is devoid of peripheral vasodilating activity while retaining glyburide-reversible cardioprotective activity. In isolated rat hearts subjected to 25 min of global ischemia and 30 min of reperfusion, BMS-191095 increased the time to onset of ischemic contracture with an EC25 of 1.5 μM, which is comparable to 4.7 μM and 3.0 μM for cromakalim and BMS-180448, resp. Comparisons of cardioprotective and vasorelaxant potencies in vitro and in vivo showed BMS-191095 to be significantly more selective for cardioprotection with virtually no effect on peripheral smooth muscle, whereas cromakalim showed little selectivity. In addition to increasing the time to the onset of contracture, BMS-191095 improved postischemic recovery of function and reduced lactate dehydrogenase release in the isolated rat hearts. The cardioprotective effects of BMS-191095 were abolished by glyburide and sodium 5-hydroxydecanoate (5-HD). BMS-191095 did not shorten action potential duration in normal or hypoxic myocardium within its cardioprotective concentration range nor did it activate sarcolemmal KATP current (≤30 μM). BMS-191095 opened cardiac mitochondrial KATP with a K1/2 of 83 nM, and this was abolished by glyburide and 5-HD. These results show that the cardioprotective effects of BMS-191095 are dissociated from peripheral vasodilator and cardiac sarcolemmal KATP activation. Agents like BMS-191095 may owe their cardioprotective selectivity to selective mitochondrial KATP activation.

IT 166095-21-2, BMS-191095
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. characterization of mitochondrial KATP opener BMS-191095)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

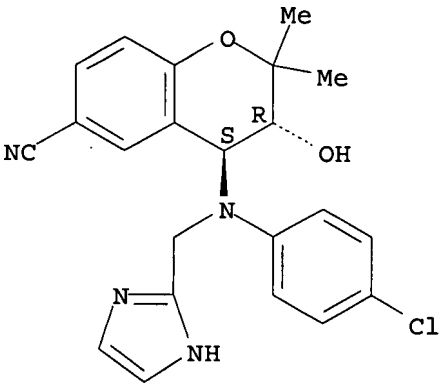
L9 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:510838 HCAPLUS
DOCUMENT NUMBER: 131:295097
TITLE: Cardioselective Antiischemic ATP-Sensitive Potassium Channel (KATP) Openers. 6. Effect of Modifications at C6 of Benzopyranyl Cyanoguanidines
AUTHOR(S): Ding, Charles Z.; Rovnyak, George C.; Misra, Raj N.; Grover, Gary J.; Miller, Arthur V.; Ahmed, Syed Z.; Kelly, Yolanda; Normandin, Diane E.; Sleph, Paul G.; Atwal, Karnail S.
CORPORATE SOURCE: The Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA
SOURCE: Journal of Medicinal Chemistry (1999), 42(18), 3711-3717
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect on potency and selectivity of modifications at the C6 position of the cardioprotective KATP opener BMS-180448 is described. Structure-activity studies show that a variety of electron-withdrawing groups (ketone, sulfone, sulfonamide, etc.) are tolerated for cardioprotective activity as measured by EC25 values for an increase in time to the onset of contracture in globally ischemic rat hearts. Changes made to the sulfonamido substituent indicate that compds. derived from secondary lipophilic amines are preferred for good cardioprotective potency and selectivity. The diisobutylsulfonamide analog (I) (EC25 = 0.04 μM) is the most potent compound of this series. The cardiac selectivity of I results from a combination of reduced vasorelaxant potency and enhanced cardioprotective potency relative to the potent vasodilating KATP openers (e.g., cromakalim). I is over 4 orders of magnitude more cardiac selective than cromakalim. These results support the hypothesis that the cardioprotective and vasorelaxant properties of KATP openers follow distinct structure-activity relationships. The mechanism of action of I appears to involve opening of the cardiac KATP as its cardioprotective effects are abolished by the KATP blocker glyburide.

IT 166095-21-2, BMS 191095
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation and cardioprotective structure-activity relations of benzopyranylcyanoguanidines as ATP-sensitive potassium channel openers)

RN 166095-21-2 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

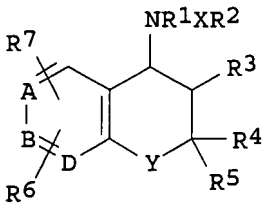


REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

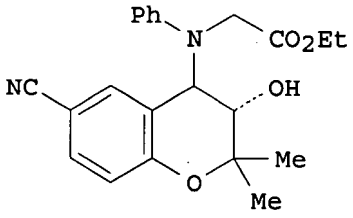
L9 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:755870 HCAPLUS
DOCUMENT NUMBER: 130:13916
TITLE: Preparation of 4-(arylamino)benzopyrans and analogs as cardiovascular agents
INVENTOR(S): Rovnyak, George C.; Atwal, Karnail S.; Santafianos, Dinos P.; Ding, Charles Z.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA
SOURCE: U.S., 43 pp., Cont.-in-part of U. S. Ser. No. 134,034, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5837702	A	19981117	US 1994-296341	19940830 <--
CA 2132766	A1	19950408	CA 1994-2132766	19940923 <--
FI 9404624	A	19950408	FI 1994-4624	19941004 <--
NO 9403763	A	19950410	NO 1994-3763	19941006 <--
ZA 9407833	A	19950413	ZA 1994-7833	19941006 <--
AU 9474461	A	19950427	AU 1994-74461	19941006 <--
HU 72447	A2	19960429	HU 1994-2884	19941006 <--
CN 1107473	A	19950830	CN 1994-116854	19941007 <--
JP 07242650	A	19950919	JP 1994-244216	19941007 <--
PRIORITY APPLN. INFO.:			US 1993-134034 B2	19931007

GI



I



II

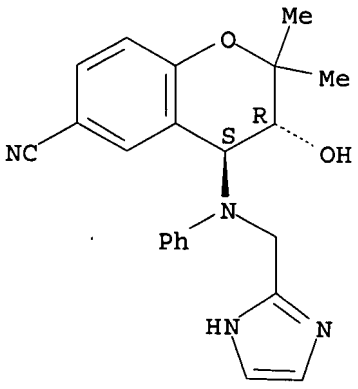
AB Title compds. [I; A, B, D = C atom (sic), or 1 of A, B, D = N or NO and the others = C atom (si); X = alkyl; XR2 = H, aryl, heterocyclyl when R1 = heterocyclyl; Y = bond, CH2, C, O, S NR8; R8 = H, alkyl, haloalkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)aryl; R1 = aryl, heterocyclyl; R2 = CO2R8, SR8, OR8, cyano, heterocyclyl, amino, aminocarbonyl, (cyclic) phosphate alkyl ester, etc.; R3 = H, OH, O2CR8; R4, R5 = H, alkyl, aralkyl; R4R5C = 5-7 membered carbocyclyl; R6 = H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, cycloalkylalkyl, cyano, NO2, COR8, CO2R8, CF3, alkylthio, alkylsulfinyl, alkylsulfonyl, (cyclic) phosphate alkyl ester, halo, amino, alkoxy, OCF3, OCH2CF3, tetrazolyl, imidazolyl, oxazolyl, triazolyl, etc.; R7 = H, alkyl, OH, alkoxy, amino, NHCOR8, cyano, NO2; n = 1-3], were prepared as potassium channel activators useful as antiischemics (no data). Thus, 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2H-benzopyran-6-carbonitrile and PhNHCH2CO2Et were stirred with Mg(ClO4)2 in MeCN for 2 days to give 53% title compound (II).

IT 166095-11-0P 166095-23-4P 166095-53-0P
166095-95-0P 166095-96-1P 166095-99-4P
166096-00-0P 166096-01-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 4-(arylamino)benzopyrans and related compds. as cardiovascular agents)

RN 166095-11-0 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-4-[(1H-imidazol-2-ylmethyl)phenylamino]-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

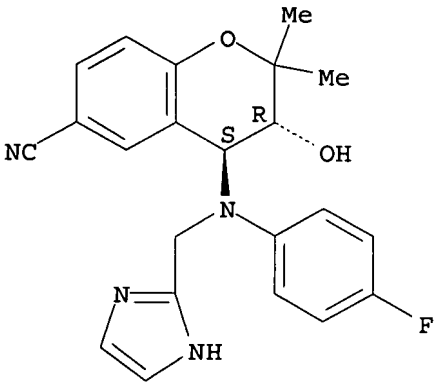


RN 166095-23-4 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA

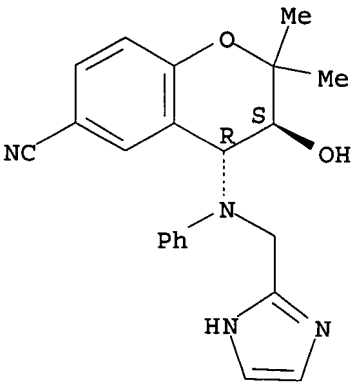
INDEX NAME)

Absolute stereochemistry.



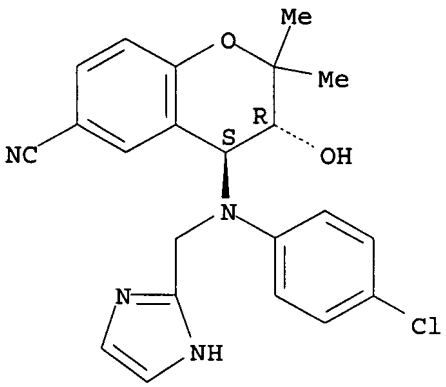
RN 166095-53-0 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-4-[(1H-imidazol-2-ylmethyl)phenylamino]-2,2-dimethyl-, (3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 166095-95-0 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, monohydrochloride, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



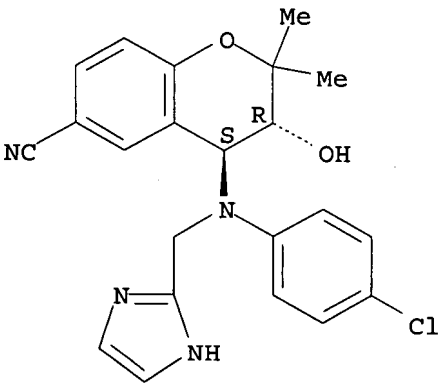
● HCl

RN 166095-96-1 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, sulfate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

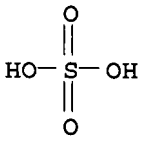
CRN 166095-21-2
CMF C22 H21 Cl N4 O2

Absolute stereochemistry.



CM 2

CRN 7664-93-9
CMF H2 O4 S

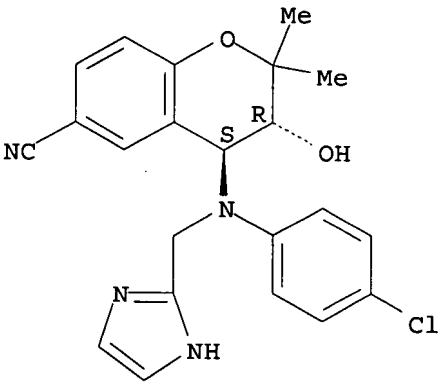


RN 166095-99-4 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

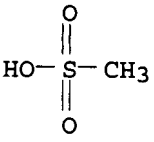
CRN 166095-21-2
CMF C22 H21 Cl N4 O2

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S

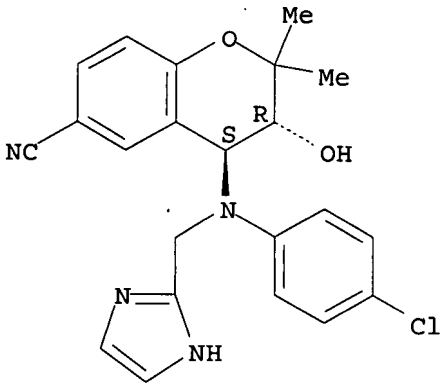


RN 166096-00-0 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, phosphate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

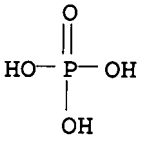
CRN 166095-21-2
CMF C22 H21 Cl N4 O2

Absolute stereochemistry.



CM 2

CRN 7664-38-2
CMF H3 O4 P

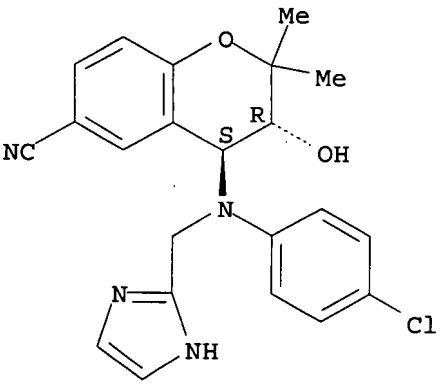


RN 166096-01-1 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, mononitrate (salt) (9CI) (CA INDEX NAME)

CM 1

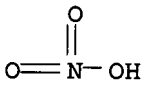
CRN 166095-21-2
CMF C22 H21 Cl N4 O2

Absolute stereochemistry.



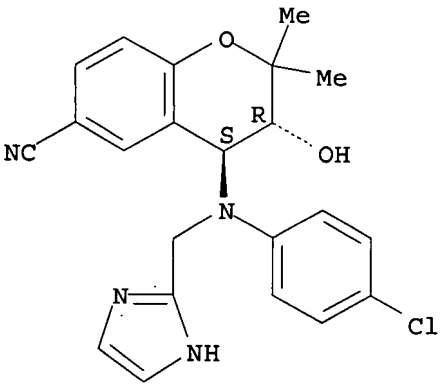
CM 2

CRN 7697-37-2
CMF H N O3



IT 166095-21-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 4-(arylamino)benzopyrans and related compds. as cardiovascular agents)
RN 166095-21-2 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



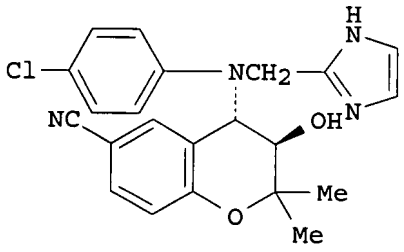
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:342006 HCAPLUS
DOCUMENT NUMBER: 127:50637
TITLE: Process for preparing 4-arylaminobenzopyrans and related compounds
INVENTOR(S): Kronenthal, David R.; Mueller, Richard H.; Godfrey, Jollie D., Jr.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: U.S., 11 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 5629429	A	19970513	US 1995-486111	19950607 <--
PRIORITY APPLN. INFO.:			US 1995-486111	19950607

OTHER SOURCE(S): CASREACT 127:50637; MARPAT 127:50637
GI



I

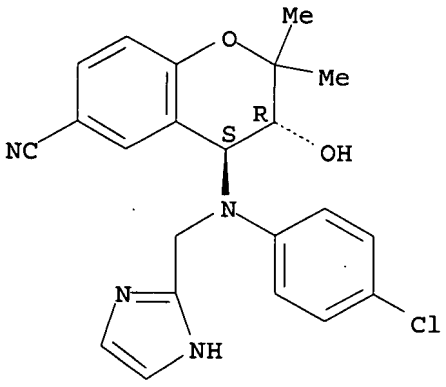
AB Title compds. are prepared by treating an arylamine with 2 equivalent of a base, followed by treatment with an epoxybenzopyran. Use of a Li base, such as BuLi, LiN(CHMe2)2, or LiN(SiMe3)2, gives predominantly the trans-arylamino(hydroxy)benzopyran, whereas use of a Grignard reagent, such as EtMgBr or EtMgCl, gives predominantly the cis-products. The products are useful as antiischemic agents and K channel activators (no data). Thus, 4-ClC6H4NH2 was treated with 2-imidazolecarboxaldehyde to give N-(4-chlorophenyl)-N-(2-imidazolylmethyl)amine which was treated with (1aR-cis)-1a,7b-dihydro-2,2-dimethyl-2H-oxireno[c]-1-benzopyran-6-carbonitrile in presence of LiN(SiMe3)2 to give the title compound I.

IT 166095-21-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stereoselective preparation of arylaminobenzopyrans by use of base)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

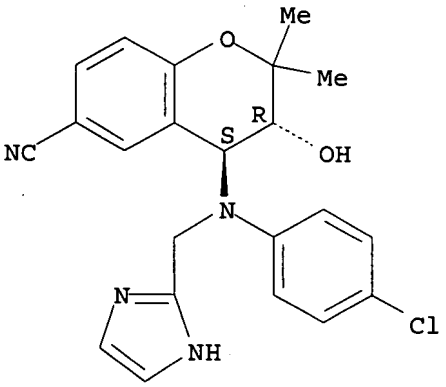
Absolute stereochemistry.



IT 166095-95-0P 186180-85-8P 190952-97-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(stereoselective preparation of arylaminobenzopyrans by use of base)

RN 166095-95-0 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, monohydrochloride, (3R,4S)- (9CI) (CA INDEX NAME)

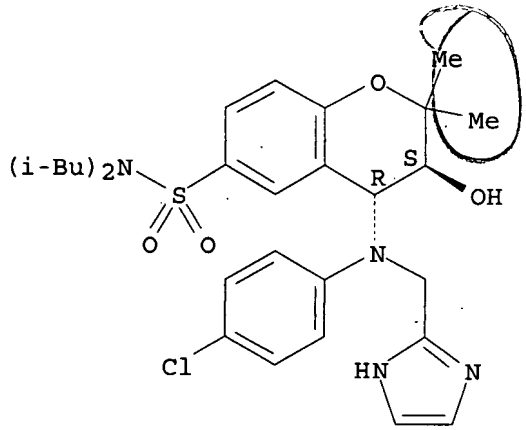
Absolute stereochemistry.



● HCl

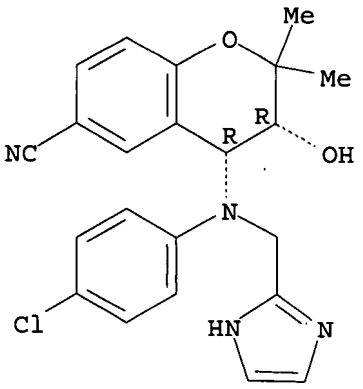
RN 186180-85-8 HCAPLUS
CN 2H-1-Benzopyran-6-sulfonamide, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-N,N-bis(2-methylpropyl)-, (3S-trans)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 190952-97-7 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R-cis)- (9CI) (CA INDEX NAME)

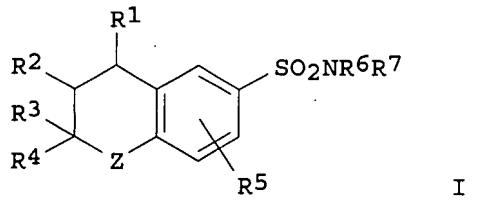
Absolute stereochemistry.



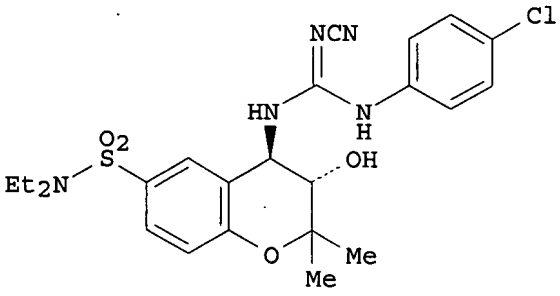
L9 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:113299 HCAPLUS
DOCUMENT NUMBER: 126:117866
TITLE: Preparation of N-(4-chlorophenyl)-N'-(sulfonamido-4-benzopyranyl)-N''-cyanoguanidines and analogs as potassium channel activators
INVENTOR(S): Ding, Charles Z.; Atwal, Karnail S.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: Eur. Pat. Appl., 55 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 747374	A1	19961211	EP 1996-109023	19960605 <--
EP 747374	B1	20011212		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 5869478	A	19990209	US 1995-481007	19950607 <--
AT 210650	T	20011215	AT 1996-109023	19960605 <--
PT 747374	T	20020531	PT 1996-109023	19960605 <--
ES 2169174	T3	20020701	ES 1996-109023	19960605 <--
CA 2178353	A1	19961208	CA 1996-2178353	19960606 <--
AU 9654762	A	19961219	AU 1996-54762	19960606 <--
AU 714432	B2	20000106		
JP 09003035	A	19970107	JP 1996-146288	19960607 <--

PRIORITY APPLN. INFO.: US 1995-481007 A 19950607
OTHER SOURCE(S): CASREACT 126:117866; MARPAT 126:117866
GI



I



II

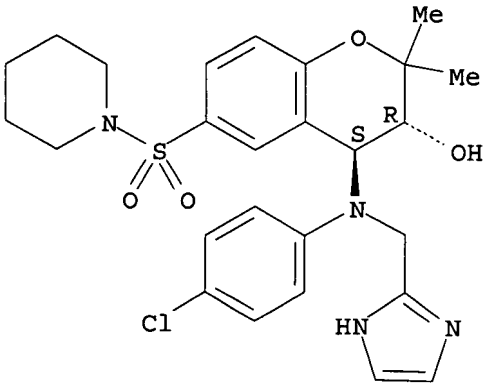
AB Title compds. [I; R1 = NR10C(:X)NR8R9, NR12Z1R13, etc.; R2 = H, OH, alkanoyloxy, etc.; R3,R4 = H or (ar)alkyl; R3R4 = atoms to complete a carbocyclic ring; R6,R7 = H, (un)substituted alkyl, aryl, etc.; NR6R7 = heterocyclyl; R5R6 = atoms to complete a ring; R8 = aryl(alkyl), heterocyclyl(alkyl); R9 = H or alkyl; R10 = H, alkyl, aryl(alkyl), etc.; R12 = aryl or heterocyclyl; R13 = H, CO2H, alkoxycarbonyl, CCONH2, etc.; X = NCN, O, S; Z = bond, CH2, CO, O, S, (alkyl)imino, etc.; Z1 = bond, alkylene] were prepared as potassium channel activators (no data). Thus, 4-BrC6H4OH was etherified by HOCMe2C.tplbond.CH and the cyclized product converted in 5 steps to (3S-trans)-4-amino-N,N-diethyl-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-sulfonamide which was condensed with 4-ClC6H4NHC(:S)NHCN to give title compound II.

IT 186180-82-5P 186180-83-6P 186180-85-8P
186255-44-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-(4-chlorophenyl)-N'-(sulfonamido-4-benzopyranyl)-N''-cyanoguanidines and analogs as potassium channel activators)

RN 186180-82-5 HCAPLUS

CN Piperidine, 1-[[4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-yl]sulfonyl]-, monohydrochloride, (3R-trans)- (9CI) (CA INDEX NAME)

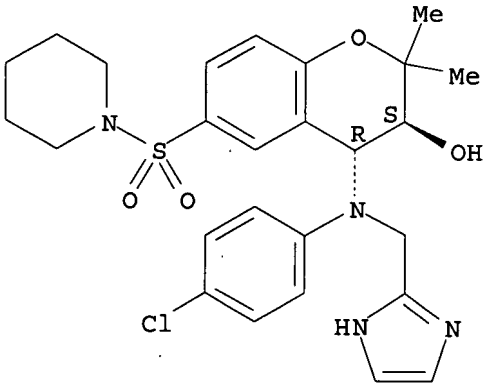
Absolute stereochemistry. Rotation (+).



● HCl

RN 186180-83-6 HCAPLUS
CN Piperidine, 1-[[4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-yl]sulfonyl]-, monohydrochloride, (3S-trans)- (9CI) (CA INDEX NAME)

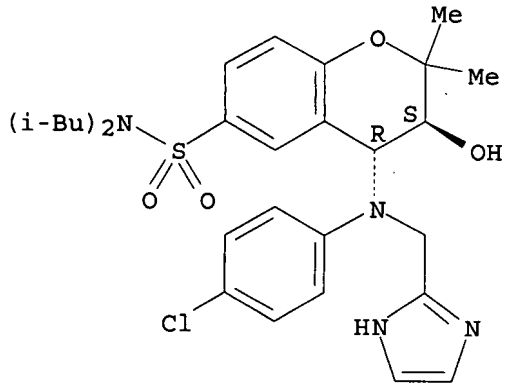
Absolute stereochemistry. Rotation (-).



● HCl

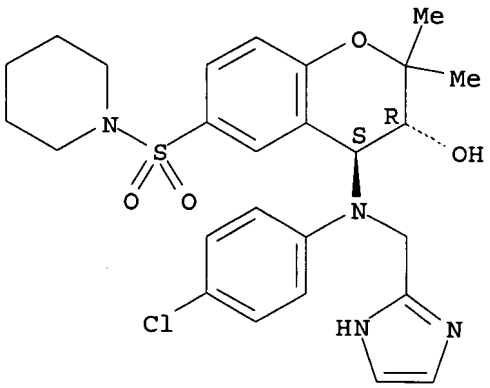
RN 186180-85-8 HCAPLUS
CN 2H-1-Benzopyran-6-sulfonamide, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-N,N-bis(2-methylpropyl)-, (3S-trans)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 186255-44-7 HCAPLUS
CN Piperidine, 1-[[(3R,4S)-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-yl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L9 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:48231 HCAPLUS
DOCUMENT NUMBER: 126:126687
TITLE: A highly selective ATP-dependent potassium channel opener mimics ischemic preconditioning protection in isolated human atrium
AUTHOR(S): Carr, C. S.; Yellon, D. M.
CORPORATE SOURCE: Hatter Institute, University College London Hospitals, London, UK
SOURCE: Medical Science Research (1996), 24(10), 651-654
CODEN: MSCREJ; ISSN: 0269-8951
PUBLISHER: Chapman & Hall
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The KATP channel has been implicated in the mechanism of ischemic preconditioning. We examined the effects of BMS 191095, a highly selective KATP channel opener, either alone or with glibenclamide (KATP channel blocker), on human atrium. Isolated human atrial trabecula superfused

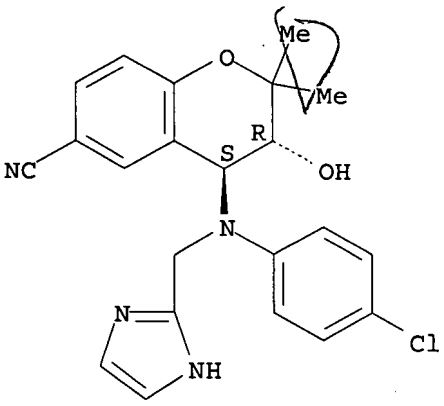
with oxygenated Tyrode's solution and paced at 1 Hz underwent one of four protocols prior to 90 min hypoxic substrate-free perfusion at 3 Hz (simulated ischemia), followed by 120 min of reoxygenation with substrate at 1 Hz (reoxygenation). Preconditioning (PC) consisted of 3 min simulated ischemia and 7 min reoxygenation. The exptl. endpoint was recovery of contractile function, presented as percentage of baseline function. BMS (45.8% ± 4.4) and PC (50.5% ± 3.6) produced similar functional recoveries following 120 min reperfusion; significantly different to controls (20.8% ± 3.5, ANOVA). Glibenclamide abolished the BMS protection (20.8% ± 4.2). This results suggest that ischemic preconditioning in humans may occur via a KATP channel opening effect.

IT 166095-21-2, BMS 191095
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(a highly selective ATP-dependent potassium channel opener mimics ischemic preconditioning protection in isolated human atrium)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:744328 HCAPLUS

DOCUMENT NUMBER: 126:98837

TITLE: Cardioselective Antiischemic ATP-Sensitive Potassium Channel (KATP) Openers. 5. Identification of 4-(N-Aryl)-Substituted Benzopyran Derivatives with High Selectivity

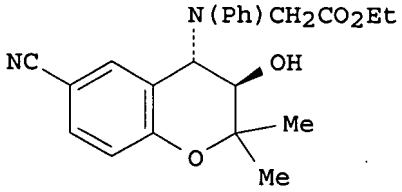
AUTHOR(S): Rovnyak, George C.; Ahmed, Syed Z.; Baird, Anne J.; Ding, Charles Z.; Dzwonczyk, Steven; Ferrara, Francis N.; Humphreys, W. Griffith; Grover, Gary J.; McLaughlin, Lee G.; et al.

CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA

SOURCE: Journal of Medicinal Chemistry (1997), 40(1), 24-34
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

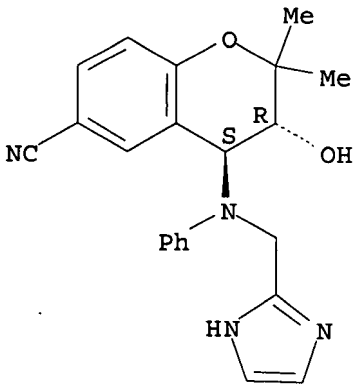
AB This paper describes our studies aimed at the discovery of structurally distinct analogs of the cardioprotective KATP opener BMS-180448 with improved selectivity for the ischemic myocardium. The starting compound I showed good cardioprotective potency and excellent selectivity compared to BMS-180448 and the first-generation KATP opener cromakalim. The structure-activity studies indicate that increasing the size of the alkyl ester leads to diminished potency as does its replacement with a variety of other groups (nitrile, Me sulfone). Replacement of the Et ester of I with an imidazole gave the best compound (BMS-191095) of this series which maintains the potency and selectivity of its predecessor I. The results described in this publication further support that there is no correlation between vasorelaxant and cardioprotective potencies of KATP openers. BMS-191095 is over 20- and 4000-fold more selective for the ischemic myocardium than BMS-180448 and cromakalim, resp. The selectivity for the ischemic myocardium is achieved by reduction of vasorelaxant potency rather than enhancement in antiischemic potency. As for cromakalim and BMS-180448, the cardioprotective effects of BMS-191095 are inhibited by cotreatment with the KATP blocker glyburide, indicating that the KATP opening is involved in its mechanism of cardioprotection. With its good oral bioavailability (47%) and plasma elimination half-life (3 h) in rats, BMS-191095 offers an excellent candidate to investigate the role of residual vasorelaxant potency of 2 toward its cardioprotective activity in vivo.

IT 166095-11-0P 166095-21-2P, BMS 191095
166095-23-4P 185690-27-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and structure-activity relations of benzopyran derivs. as cardioselective antiischemic ATP-sensitive potassium channel openers)

RN 166095-11-0 HCAPLUS

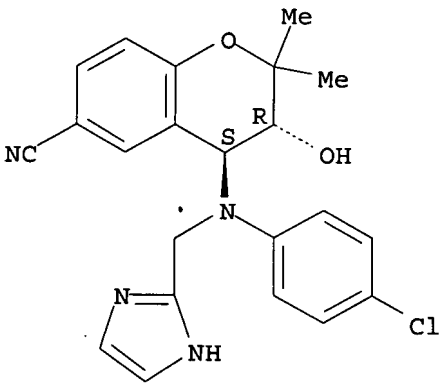
CN 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-4-[(1H-imidazol-2-ylmethyl)phenylamino]-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



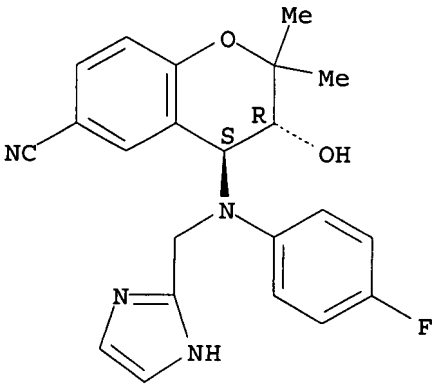
RN 166095-21-2 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



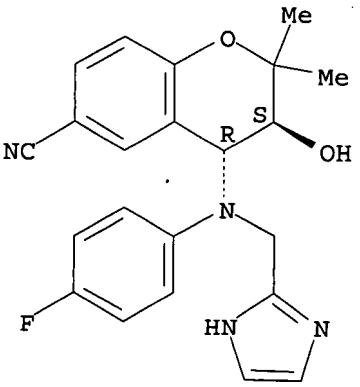
RN 166095-23-4 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 185690-27-1 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3S-trans)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:728999 HCAPLUS
DOCUMENT NUMBER: 123:339740
TITLE: Preparation of 4-(arylamino)benzopyrans and related compounds as cardiovascular agents.
INVENTOR(S): Rovnyak, George C.; Atwal, Karnail; Santafianos, Dinos P.; Ding, Charles Z.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA
SOURCE: Eur. Pat. Appl., 66 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

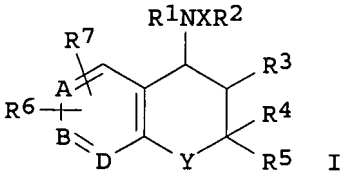
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 648758	A1	19950419	EP 1994-306814	19940916 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE

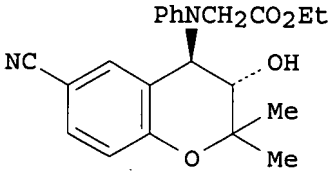
CA 2132766	A1	19950408	CA 1994-2132766		19940923 <--
FI 9404624	A	19950408	FI 1994-4624		19941004 <--
NO 9403763	A	19950410	NO 1994-3763		19941006 <--
ZA 9407833	A	19950413	ZA 1994-7833		19941006 <--
AU 9474461	A	19950427	AU 1994-74461		19941006 <--
HU 72447	A2	19960429	HU 1994-2884		19941006 <--
CN 1107473	A	19950830	CN 1994-116854		19941007 <--
JP 07242650	A	19950919	JP 1994-244216		19941007 <--
PRIORITY APPLN. INFO.:			US 1993-134034	A	19931007

OTHER SOURCE(S): MARPAT 123:339740

GI



I



II

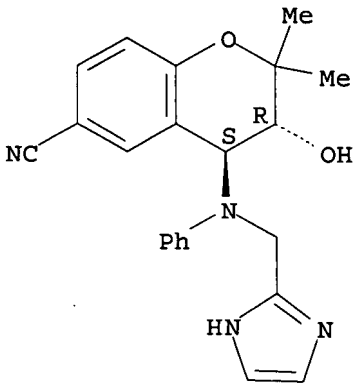
AB Title compds. [I; A, B, D = C, or 1 of A, B, D = N, NO and the others = C; X = alkyl; XR2 = H, aryl, heterocyclyl when R1 = heterocyclyl; Y = bond, CH2, C(O), O, S N(R8); R8 = H, alkyl, haloalkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)aryl; R1 = aryl, heterocyclyl; R2 = CO2R8, SR8, OR8, cyano, heterocyclyl, amino, aminocarbonyl, (cyclic) phosphate alkyl ester, etc.; R3 = H, OH, O2CR8; R4, R5 = H, alkyl, aralkyl; R4R5C = 5-7 membered carbocyclyl; R6 = H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, cycloalkylalkyl, cyano, NO2, COR8, CO2R8, CF3, alkylthio, alkylsulfinyl, alkylsulfonyl, (cyclic) phosphate alkyl ester, halo, amino, alkoxy, OCF3, OCH2CF3, tetrazolyl, imidazolyl, oxazolyl, triazolyl, etc.; R7 = H, alkyl, OH, alkoxy, amino, NHCOR8, cyano, NO2; n = 1-3], were prepared as potassium channel activators useful as antiischemics (no data). Thus, 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2H-benzopyran-6-carbonitrile and PhNHCH2CO2Et were stirred with Mg(ClO4)2 in MeCN for 2 days to give 53% title compound (II).

IT 166095-11-0P 166095-23-4P 166095-53-0P
166095-95-0P 166095-96-1P 166095-99-4P
166096-00-0P 166096-01-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 4-(arylamino)benzopyrans and related compds. as cardiovascular agents)

RN 166095-11-0 HCAPLUS

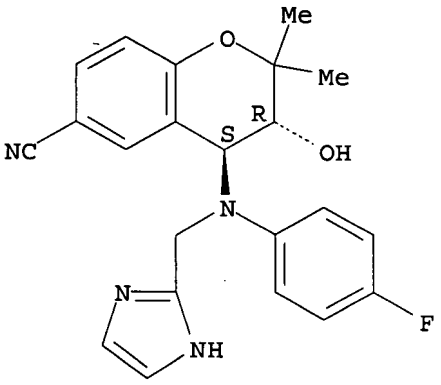
CN 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-4-[(1H-imidazol-2-ylmethyl)phenylamino]-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



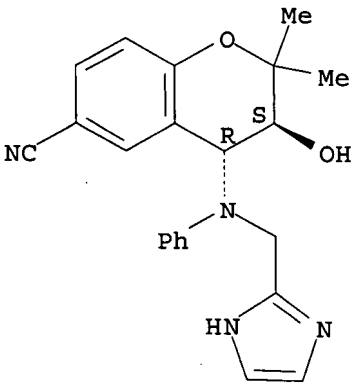
RN 166095-23-4 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



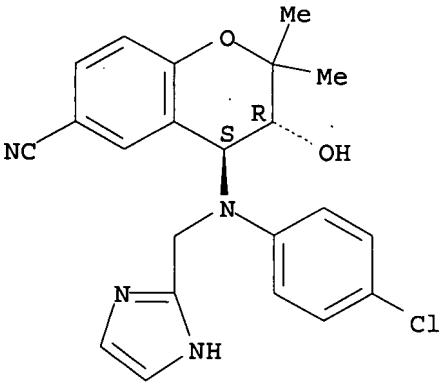
RN 166095-53-0 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-4-[(1H-imidazol-2-ylmethyl)phenylamino]-2,2-dimethyl-, (3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 166095-95-0 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, monohydrochloride, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



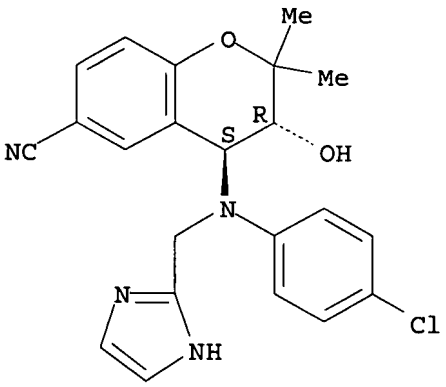
● HCl

RN 166095-96-1 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, sulfate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

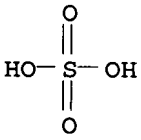
CRN 166095-21-2
CMF C22 H21 Cl N4 O2

Absolute stereochemistry.



CM 2

CRN 7664-93-9
CMF H2 O4 S

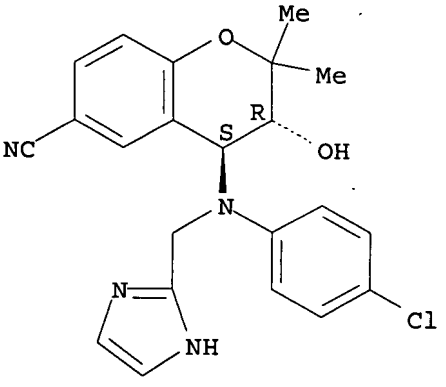


RN 166095-99-4 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

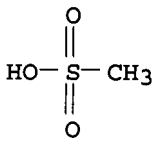
CRN 166095-21-2
CMF C22 H21 Cl N4 O2

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S

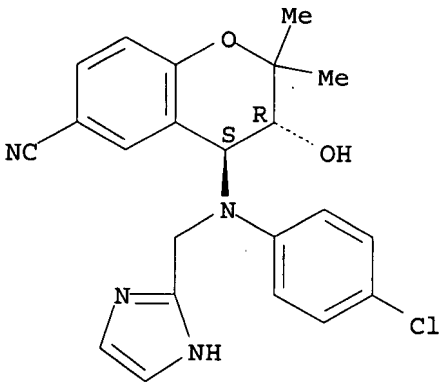


RN 166096-00-0 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, phosphate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

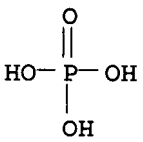
CRN 166095-21-2
CMF C22 H21 Cl N4 O2

Absolute stereochemistry.



CM 2

CRN 7664-38-2
CMF H3 O4 P

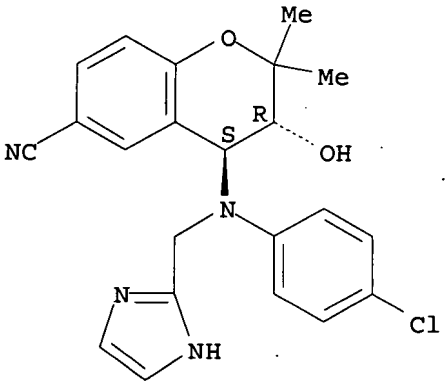


RN 166096-01-1 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, mononitrate (salt) (9CI) (CA INDEX NAME)

CM 1

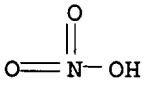
CRN 166095-21-2
CMF C22 H21 Cl N4 O2

Absolute stereochemistry.



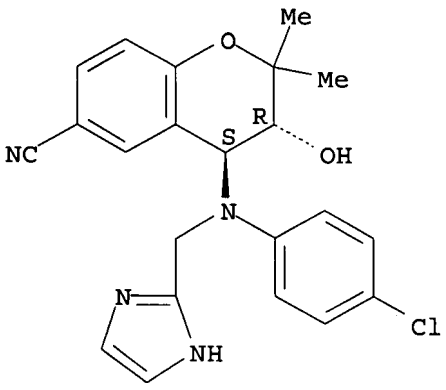
CM 2

CRN 7697-37-2
CMF H N O3



IT 166095-21-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 4-(arylamino)benzopyrans and related compds. as cardiovascular agents)
RN 166095-21-2 HCAPLUS
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	115.80	462.01

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-15.60	-15.60

STN INTERNATIONAL LOGOFF AT 14:39:13 ON 20 APR 2007